This is a digital copy of a book that was preserved for generations on library shelves before it was carefully scanned by Google as part of a project to make the world's books discoverable online.

It has survived long enough for the copyright to expire and the book to enter the public domain. A public domain book is one that was never subject to copyright or whose legal copyright term has expired. Whether a book is in the public domain may vary country to country. Public domain books are our gateways to the past, representing a wealth of history, culture and knowledge that's often difficult to discover.

Marks, notations and other marginalia present in the original volume will appear in this file - a reminder of this book's long journey from the publisher to a library and finally to you.

Usage guidelines

Google is proud to partner with libraries to digitize public domain materials and make them widely accessible. Public domain books belong to the public and we are merely their custodians. Nevertheless, this work is expensive, so in order to keep providing this resource, we have taken steps to prevent abuse by commercial parties, including placing technical restrictions on automated querying.

We also ask that you:

+ *Make non-commercial use of the files* We designed Google Book Search for use by individuals, and we request that you use these files for personal, non-commercial purposes.

+ *Refrain from automated querying* Do not send automated queries of any sort to Google's system: If you are conducting research on machine translation, optical character recognition or other areas where access to a large amount of text is helpful, please contact us. We encourage the use of public domain materials for these purposes and may be able to help.

+ *Maintain attribution* The Google "watermark" you see on each file is essential for informing people about this project and helping them find additional materials through Google Book Search. Please do not remove it.

+ *Keep it legal* Whatever your use, remember that you are responsible for ensuring that what you are doing is legal. Do not assume that just because we believe a book is in the public domain for users in the United States, that the work is also in the public domain for users in other countries. Whether a book is still in copyright varies from country to country, and we can't offer guidance on whether any specific use of any specific book is allowed. Please do not assume that a book's appearance in Google Book Search means it can be used in any manner anywhere in the world. Copyright infringement liability can be quite severe.

About Google Book Search

Google's mission is to organize the world's information and to make it universally accessible and useful. Google Book Search helps readers discover the world's books while helping authors and publishers reach new audiences. You can search through the full text of this book on the web at `http://books.google.com/`

THE PROTÉAL TREATMENT OF

CANCER AND ALLIED CONDITIONS

A PRACTICAL STUDY OF A NEW THERAPEUTIC PRINCIPLE AS INTERPRETED IN THE LIGHT OF THE PROTEOMORPHIC THEORY

BY

HENRY SMITH WILLIAMS, M.D., LL.D.

With the Compliments

of

The Author

LANE LIBRARY

PUBLISHED DECEMBER 1ST, 1916

NEW YORK

THE GOODHUE COMPANY

Digitized by Google

This monograph

telling of a humanitarian work that vitally concerns the lives and welfare of one-sixteenth of the world's total population,—a work carried forward in the face of fanatical opposition, under almost insuperable difficulties, and at great personal sacrifice,—

is dedicated

to the memory of five of my New England ancestors—representing four patronymic generations in direct line—who were Regular physicians of distinction, namely:

(1) My great great grandfather, THOMAS WILLIAMS, A.M. (Yale), M.D. (1718-1775), Colonial surgeon in the French and Indian wars and brother of the founder of Williams College; my great grandfathers (2) WILLIAM STODDARD WILLIAMS, M.D. (1762-1828), of Deerfield, Mass., and (3) JOSEPH GOODHUE, M.D., of Portsmouth, surgeon in the Federal Army; (4) my grandfather, STEPHEN WEST WILLIAMS, A.M., M.D. (1790-1856), Professor and Lecturer upon Medical Jurisprudence, the Theory of Medicine, and Medical Botany, in the Berkshire Medical Institute, in the College of Physicians and Surgeons in New York, in Dartmouth College, and in Willoughby University; author of numerous books; personal friend of Valentine Mott and Oliver Wendell Holmes; close associate of N. S. Davis in the organization of The American Medical Association; and (5) EDWARD JENNER WILLIAMS, M.D. (1823-1881), my father, a man endowed with rare qualities of mind matched by yet rarer qualities of heart:

Each of them perennially active in the service of humanity; each of them in the forefront of the medical progress of his time; each of them a life-long zealot for the best traditions of medical ethics; each of them honored by all who knew him in life, and in death epitaphed simply and justly with the words:

"He was a skillful practitioner and an honest man."

Copyright, 1916
THE GOODHUE COMPANY

Digitized by Google

261
172
1916

FOREWORD

The Proteal treatment of cancer and allied conditions of disturbed protein metabolism is a new type of medication. The time has not yet come for final appraisal of its value, but certain definite statements regarding it may be made, based on the observations of about 1,200 physicians dealing with more than 3,000 cases of cancer of various types in the human subject.

"Proteal" is a new word suggested by the present writer. It is a generic term implying a vegetable protein or combination of proteins used as a hypodermic medicament to combat disease. The first form of proteal to be used extensively was a combination of twelve non-toxic vegetable proteins extracted from a compound the formula for which originated with the Hungarian-American chemist, Alexander S. Horovitz, Ph.D., first publication of which was made in the *New York Medical Journal* of May 15, 1915, by Dr. Silas P. Beebe, of New York. In recent months, extensive observations have been made on cancer and other maladies treated with a variety of vegetable proteins of quite different origin, originated and first tested at the Beebe-Williams Clinic, including alfalfa proteins, rapeseed protein, and hempseed protein, used singly or in combination.

One purpose of the present monograph is to state, as clearly as may be, the result of these observations, particularly as applied to malignant neoplasms, thereby bringing to as wide a medical audience as possible a knowledge of the fact that a new form of treatment is available which enables the practitioner to offer to the sufferer from cancer—even in the inoperable stage—possible benefits that have not hitherto attended, at least in commensurate degree, any known form of medication or manipulation.

The original proteal extract was given the technical name of Autolysin,—suggested by the fact that the compound, when hypodermically administered, produces a systemic response that results in a seeming autolysis of cancer cells. Even the distinguished pathologist who suggested the name would probably not urge that it is a very appropriate one, for of course the destruction of cancer cells by bodily enzymes cannot in strict propriety be termed autolysis. But the name has obvious convenience and, since it appears in the literature of the subject, it may as well

9411

Digitized by Google

be retained. In the present monograph, the compound will be referred to indifferently as "Autolysin," "the original proteal mixture," and "the Beebe-Borovitz proteal remedy."

Names aside, the mixed proteals in question are extracted from a combination of herbs regarding which there has been at no time the slightest secret, and the full working formula for preparation of the extract has been published in the *New York Medical Journal.* The preparation has been distributed solely through the medical profession in the most ethical manner. Meantime of course any physician is at liberty to make the extract in his own laboratory, and any pharmaceutical house may make it for commercial distribution.

The original method of preparation of Autolysin has been twice modified. The first modification consisted in the evaporation of a large part of the alcohol, producing a more concentrated solution. This involved precipitation of a large part of the proteins soluble only in alcohol and of most of the chlorophyll. Proteins soluble in salt solution constituted the essential part of the extract, which was known as Special Concentrated Autolysin.

The more recent improvement consists of submitting the original powder to saline extraction, subsequently neutralizing the extract with sodium hydroxid. The omission of the alcohol and the neutralization of the extract make the preparation relatively painless on hypodermic administration. This form of the extract is now being used to the practical exclusion of the earlier ones.

All of the above extracts are made from the original powder devised by Dr. Horovitz, the formula for which was published by Dr. Beebe in the *New York Medical Journal* of May 15th, 1915. The constituents are the following: *Menyanthes trifoliata,* buckbean (leaves); *Melilotus officinalis,* sweet clover (leaves); *Mentha crispa,* mint (leaves); *Brassica alba,* mustard (seeds); *Anemone hepatica,* liver leaf (leaves); *Viola tricolor,* pansy (flowers and leaves); *Anthemis nobilis,* camomile (leaves); *Citrullus Colocynthis,* colocynth (fruit); *Quassia amara,* quassia (wood); *Urtica dioica,* nettle (whole plant except root); *Rheum officinale,* rhubarb (root), and *Hyssopus officinalis,* hedge hyssop (whole plant except root). The working formula and full methods of preparation are published in detail in the present volume.

The remaining proteals referred to in this monograph are those extracted from various vegetable products at the Beebe-Williams Clinic in our private experimental laboratory. As above noted, the ones hitherto used most extensively comprise the proteins of alfalfa seed, rape seed, and hemp seed. A full account of the methods of preparation is given in the text. These extracts have been used extensively since July, 1916, at the Beebe-Williams Clinic and by a few associated physicians.

Digitized by Google

Of the twelve hundred physicians who have used the original proteal compound in the treatment of about 3,000 cases of cancer, not one has published a word of disparagement of the remedy, or of doubt as to its efficacy. Criticisms have been published—but not in any case by any one claiming to have administered a single dose of autolysin to a human subject.

Without exception the physicians who have personally tested the remedy and published the results of their experience, have spoken with enthusiasm in its praise. That, assuredly, is an amazing record. I doubt that it finds a parallel in the history of any other new form of important medication whatsoever.

That proteals, properly administered, assuage the pain of the cancer sufferer in a large proportion of cases; neutralize malodor; stimulate the blood count and with it the manifestations of improved health and comfort; and in a conspicuous proportion of cases cause unmistakable modifications in the condition of the neoplasm itself, amounting frequently to marked regression—is scarcely more open to-day to dispute than that digitalis stabilizes the heart beat, that quinine antagonizes the plasmodium of malaria, or that mercury combats the germ of syphilis.

There remains, however, a question as to the amount of benefit that may be expected in any individual case; and the all important question as to whether seeming recoveries under the proteal treatment are complete and permanent recoveries. These questions will be discussed in the ensuing pages, but with no suggestion that a final answer as to the permanency of seeming cures can be made except after the lapse of a long period of time.

But if the question of the possible cure of cancer by the new type of medication must be left in abeyance, there is no occasion for delay in spreading broadcast the knowledge that the proteals bring a message of new hope for the cancer sufferer, whatever the form or stage of progress of his malady. The proteal remedies have already conferred unique benefits upon not far from 3,000 sufferers; they have been responsible for an enormous alleviation of pain in the aggregate, and for a notable extension of human lives.

Meantime no one of the hundreds of physicians who have used the original proteal mixture has suggested, so far as I am aware, that the new remedy has in any case produced harmful results tending to shorten the patient's life. At worst, the remedy has proved ineffective and harmless; at best, it has proved a boon to the patient and his friends.

It is in the highest degree satisfactory to be able to record that the remedy which possesses this unique influence over the progress of malignant neoplasms has been from the outset available

Digitized by Google

without money and without price for the treatment of every indigent cancer sufferer whose physician might ask for it.

The widely heralded statement that the remedy would be supplied just as freely for those that could not pay at all as for those of ample means, has been lived up to not only in letter but in spirit.

No cancer sufferer anywhere in the world has been denied the benefactions of the new treatment for lack of money.

The present work is constructive rather than argumentative. It is chiefly concerned, not with a particular remedy, but with a new order of things in therapeutics. It endeavors to point the way to a generalized method of non-specific protein therapy that should be applicable far outside the bounds of the cancerous condition. A body of new evidence is presented that has not hitherto been published; in particular the findings of microscopists and pathologists in support of clinical observations of proteal therapy. There is also suggested a new interpretation of the cancerous condition; and a new classification of protein antigens in general, whether used as specific or non-specific stimuli to the bodily activities.

These aspects of the subject will appeal more particularly to a limited number of the profession. But there is ample warrant for their inclusion here, because they give support to the main thesis as to the treatment of cancer and suggest practical measures for warding off the malady in the beginning and preventing recurrence in post-operative cases.

According to recent statistics, cancer accounts for five or six per cent. of all deaths. That is equivalent to saying that at least five million people are living in the United States to-day who must die of cancer unless medical science in the coming years deals more effectively with the malady than it has known how to do in the past.

I dare to hope that the facts cited in this monograph justify the belief that we are beginning to see a little light in this dark field.

I dare even to hope that the *beginning* of the end of the cancer scourge is at hand. Proteal treatment may not offer the final solution of the cancer problem; but I verily believe that it points the way to a solution.

In any event, the proteal treatment offers to-day a hitherto unattainable measure of solace, and a message of new hope for cancer sufferers everywhere in the world.

It remains for the medical profession to say whether the benefactions of the new treatment shall be available for cancer sufferers everywhere in the course of a few months; or whether the new method must continue to fight its way against fanatical opposition of medieval type, strangely anachronistic in the Twentieth Century.

Digitized by Google

THE PROTEAL TREATMENT OF CANCER

PART I

THE PRINCIPLES OF NON-SPECIFIC PROTEIN THERAPY

In the *New York Medical Journal* for October 2, 1915, I presented a study of one aspect of the cancer problem as interpreted in the light of an original theory of immunity previously published somewhat in detail and characterized as the Proteomorphic Theory. In the course of that article I indicated that my studies of cancer were guided by a new theory as to the conditions associated with the malady, and I very briefly characterized the nature of malignant neoplasms, as the new theory conceived it.

In a second paper, contributed to the *New York Medical Journal* of November 13, 1915, I summarized the preliminary results of a new treatment for inoperable cancer somewhat in detail, as applied to 766 cases treated by about 150 different physicians.

The present monograph might advantageously be read in connection with the papers of October 2 and November 13, and also in connection with the fuller exposition of the Proteomorphic Theory, as originally published in *American Medicine* of October and November, 1914.

To make the matter clearer to those who have not seen these papers, I may say that the essential features of the Proteomorphic Theory include the assumption that the chief immunization mechanism of the body is comprised in the blood and the blood-forming organs; and that immunization is associated with the activities of the leucocytes and red blood corpuscles, the former producing enzymes that begin the dissociation of the protein molecule, and the latter completing that dissociation (to the amino-acid stage) and removing waste products or toxic residues of protein metabolism by way of the liver and kidneys.

The entire subject of immunization is conceived to be identical with the subject of protein metabolism; immunization against particular bacteria being only a special case within the general law.

It must not be supposed that in associating the question of the nature and origin and treatment of cancer with the question of

Digitized by Google

immunization there is implied the conception of the germ-origin of cancer. No such assumption is made. On the contrary, I altogether disbelieve in the germ origin of cancer, and the entire theory on which I am working is opposed to that assumption. But the fact that the neoplasms associated with the cancerous condition are proteid bodies, and that bacteria are also proteid bodies, establishes a certain affinity between the two conditions, and brings both within the scope of the Proteomorphic Theory.

The present monograph may be regarded as the epitome of the comprehensive study presented in one section of my forthcoming book entitled, *The Proteomorphic Theory and the New Medicine*. Limitations of space make it essential that I should speak here with dogmatic brevity. The presentation will necessarily have the character of a synopsis rather than of full treatment, and a good many rather startling propositions will be propounded that may tend to excite controversy, and invite discussion. Needless to say, full discussion will be given in the appropriate place; here I must be content to summarize, in a fashion more didactic than I could wish, my theories and practical observations as to the nature, origin, prevention, and treatment of cancer.

Lest the sequence of subjects may suggest that this monograph is chiefly theoretical, I would hasten to assure the reader that in its chief import it is eminently practical. I discuss first the nature and origin of cancer, according to my conception, simply because it is essential that these should be understood before a clear comprehension can be had of the essential nature of the treatment, which, in my judgment, is opening the way to a practical solution of the cancer problem.

I may add that, whereas this monograph will deal chiefly with results already achieved, it comprises also the first publication of an outline of laboratory studies the ultimate value of which can be appraised only after a prolonged period of clinical observation.

A Summary of the Proteomorphic Theory

Perhaps it will be well to give a somewhat more precise idea of the purport of the Proteomorphic Theory by quoting the summary of its theses as given at the conclusion of the original article in *American Medicine* of November, 1914, as follows:

"(1) The chief mechanism of the body is the cytogenic [homatopoietic] mechanism, of which the recognized members are the bone marrow, the spleen, and the lymphatic system. The active agents through which the process of immunization is carried out are the leucocytes and red blood corpuscles generated in the various organs of this system.

"(2) The prime functions of the leucocyte, after it becomes a freely moving cell, is to facilitate and complete protein cleavage

Digitized by Google

or digestion, preparing for assimilation (to the limit of its capacity) all foreign proteins that enter the blood stream. In pursuance of this function, it is provided with digestive enzymes, and with a mechanism for the production of special types of proteolytes to cleave an endless variety of protein molecules and to counteract toxic proteins or enzymes due to bacterial activities.

"(3) The red blood corpuscle completes the hydrolysis of polypeptid and allied protein products that find their way into the blood stream. It absorbs or counteracts the toxic residual molecules that are not completely hydrolyzed; and it antagonizes the products of bacterial activity, producing antitoxins. When ultimately autolyzed or destroyed, chiefly in the liver, it gives its protein and enzymes to the blood stream, and its waste products are discharged from the body through the bile duct and the kidneys.

"(4) The chief work of synthesizing protein out of amino-acids in the organism resides with the mother cells of the cytogenic apparatus—notably with bone marrow and the spleen. But the cells of each specialized tissue—muscles, brain, glands—can on occasion synthesize each its own special type of protein, utilizing the amino-acid building materials. Each tissue can also, on occasion, hydrolyze nitrogenous molecules of the polypetid order, and give out antitoxic ferments in response to specific toxins. But as a rule the tissues are shielded by the red blood corpuscles from the necessity of performing these functions.

"(5) The vast multitudes of red corpuscles, with an aggregate bulk of about four pounds in the ordinary body, their substance having been synthesized by the mother cells out of amino-acids, constitute the chief source of the specific proteins in the blood stream, which proteins on being decompounded (with the aid of the lymphocytes) are the prominent sources of bodily energy.

"(6) Every cell that can unite with a foreign proteid product can produce an 'anti-body' calculated to antagonize that product. The leucocytes and red blood corpuscles are the particular cells that come most in contact with such foreign bodies, and they are therefore the chief source of specific proteolytes and antibodies directed against the invaders. The presence in the blood stream of these specific proteolytes and antibodies, secreted by the leucocytes and red cells, and to a certain extent by the body-cells (backed up by the presence of an adequate army of leucocytes and red cells themselves, capable of producing more of the antibodies under stimulus of invasion), constitutes the condition of immunity.

"(7) Immunization to bacterial disease is merely a special case of protein assimilation. It has in the past been as necessary to acquire immunization against the dietetic proteins—eggs, beef, mutton, chicken, fish—and against 'benign' bacteria as against the most virulent bacteria.

Digitized by Google

"(8) So-called harmless or benign bacteria are those that have been long with us, and which, therefore, the leucocytic mechanism has learned adequately to combat and control. Virulent bacteria are the relatively rare ones or those that have visited us infrequently. A relatively benign bacterium may become malignant, however, through changed conditions leading it to ingest unwonted types of protein; or through developing exceptional vigor; or through invading the system in excessive numbers.

"(9) Protein anaphylaxis of any type (including 'serum disease') is merely a special case of protein intoxication, strictly homologous with protein poisoning from the toxins of virulent bacteria. It results when a general proteolytic (leucocytic) enzyme is present in sufficient quantity to hydrolyze the foreign protein partly, while the red-cell mechanism is temporarily exhausted, so that cleavage cannot be completed, and the tissue cells are attacked. Protein anaphylaxis is strictly homologous with protein immunization. They are different aspects of the same subject corresponding respectively to the 'passive phase' and the 'active phase' of Wright's 'opsonic index.'

"(10) The activities of the cytogenic system, leading to an increase in the number of blood corpuscles and a stimulus to the activities of the individual corpuscles; and through these to completed protein assimilation and immunization, are governed in part by hormonic stimuli; the internal secretions actively engaged including those of the adreno-thyroid system and secretin from the duodenum.

"(11) The cytogenic system (including the bone marrow, the spleen, and the lymphatic glands) is a highly important member of the endocrinous system; the detached blood corpuscles are to be regarded as still a part of that system; and the study of the system as a whole offers a fruitful field for discovery of new methods in immunization and the treatment of infectious diseases.

"(12) The general theory of the action of the cytogenic system above outlined finds support in clinical observations of disease and in empirical therapy; and the theory itself gives important clues to the scientific application of old and new therapeutic measures, including an extension of serum-therapy and vaccine-therapy and the development of a new cyto-therapy."

New Application of the Proteomorphic Principle

At the time when the Proteomorphic Theory was first published, in October, 1914, I had small expectation that so novel a doctrine would receive early acceptance. The usual history of the introduction of new ideas is that they lie dormant for a good many years after first being suggested, and are then exhumed and given currency because they have found support in newly discovered series of facts. It would not have been in the least sur-

Digitized by Google

prising had the main contentions of the Proteomorphic Theory been quite ignored by phsiologists and pathologists in general for a dozen or score of years.

But it chanced that within a few months after the publication of the theory, a new set of facts was available, of which I had not the remotest inkling at the time when the theory was evolved. The facts had to do with the results attained in the treatment of cancer, with vegetable proteins, as advocated by Dr. Silas P. Beebe, then Professor of Experimental Therapeutics in Cornell University Medical School. In studying at first hand the results of this treatment, I was made cognizant of a body of new evidence that fitted in with the chief tenets of the Proteomorphic Theory as harmoniously as if the theory itself had been devised for the interpretation of these facts.

The vegetable proteins in question were extracted from a rather bizarre combination of twelve familiar plants, most of which are little used in modern pharmacology, namely: *Menyanthes trifoliata, Melitotus officinalis, Mentha crispa, Brassica alba, Anemone hepatica, Viola tricolor, Anthemis nobilis, Citrullus colocynthis, Quassia amara, Urtica dioica, Rheum officinale, Hyssopus officinalis.* This compound, formulated by Alexander S. Horovitz, Ph.D. of Budapest and New York, had previously been used as a poultice in the treatment of superficial malignant growths.

The extract made with salt solution and alcohol contained lipoids, vegetable salts, and chlorophyll as well as plant proteins. From first-hand study of its effects, I was soon convinced that it had the peculiar property, when administered hypodermically, of developing a systemic condition antagonistic to the cells of malignant neoplasms, causing such cells, in favorable cases, to undergo seeming autolysis.

In the article in the *New York Medical Journal* of October 2, 1915, and in a second article published in the same periodical under date of November 13th, 1915, I had occasion to suggest a theory of action of the new remedy on one hand and to summarize the statistical evidence for its efficacy on the other; the summary including the report of results attained in the treatment of 762 cases of inoperable cancer by 142 physicians working independently. This statistical presentation was demonstrative, I believe, as to the peculiar efficacy of the extract in ameliorating the unfavorable symptoms of cancer cases. With that aspect of the matter, however, I am not primarily concerned in the present monograph. For the moment we are concerned with clinical facts only in so far as they furnish the background for the theoretical interpretation of a new therapeutic principle illustrated not merely by the original vegetable protein extract but by a series of other vegetable and animal protein solutions devised by Dr. Silas P.

Digitized by Google

Beebe and myself, further details as to which will appear as we proceed.

Although the paper of October 2, 1915, above referred to, had to do specifically with the interpretation of the action of the vegetable proteins in question in their relation to malignant neoplasms, clear intimations were given that the therapeutic principle believed to be involved had much wider application. The action of the extract was explained as chiefly due to its protein content (the relatively non-toxic vegetable proteins acting as antigens to stimulate the enzymic activities of the corpuscles and new corpuscle-production by the cytogenic apparatus), and the conclusion was expressly stated that: the remedy "is not merely a cancer remedy; it is a remedy against all protein infections."

I further stated my belief that in the attempt to explain the rationale of the action through which the vegetable proteins bring about a beneficent increase in the armies of leucocytes and erythrocytes, "we shall gain glimpses of an entirely new field of therapeutics, and shall be enabled to give at least a proximal explanation of the exact manner of action of a remedy, the introduction of which, I believe, constitutes the inauguration of a method that must in future rank with serum therapy and vaccine therapy—if, indeed, it does not altogether outstrip or totally supplant both these relatively new additions to the equipment of the practical physician."

Such a view as this, if presented without both theoretical and clinical backing, must have seemed heretical. It carried the clear implication that a non-specific protein might serve as an antigen stimulating the production of "specific" enzymes or anti-bodies capable of decompounding proteins of many types, including the bodies of various pathogenic bacteria and various types of "malignant" cells.

Such a suggestion ran counter to the dominant medical thought of the moment. The familiar facts regarding diphtheria antitoxin, Wright's anti-typhoid vaccine and allied vaccines, and Ehrlich's salvarsan (to mention typical examples of three new types of medication) had revived in the mind of the profession the old hope that specific medication was to give final answer to all therapeutic problems. In the cancer field, as well as in the field of bacteria, recent effort had nearly all been directed along the lines either of specific antigens or of remedies having elective affinity for cancer cells. Beebe and Berkeley's attempt to develop a cancer anti-serum; Vaughan's use of residual products of the cancer cell; and Hodenpyl's use of ascitic fluid of a cancer subject were typical illustrations of one method; and the collodial copper treatment of Leo Loeb and the selenium experiments of Ehrlich and Wasserman were illustrations of the other.

Digitized by Google

It may fairly be said that most workers in the field were so thoroughly imbued with the idea of specific therapy as to cause them to look askance at any suggestion of a more general method.

Perhaps I cannot better illustrate this than by stating that among the medical men who were most closely concerned with the introduction of vegetable protein treatment, there were those who were inclined to believe that the extract would be found to contain something having a selective affinity for cancer cells, and hence falling within the scope of specific medication. These men looked with more or less doubt on the theoretical interpretation of the action of the Horovitz-Beebe remedy that I presented in the paper of October 2, 1915, and did not for some time thereafter accept the view that a general principle of protein antagonism had been invoked.

Wide Acceptance of the Proteomorphic Principle

Meantime, however, it is evident that the main features of the Proteomorphic Theory, and its detailed application in the paper above referred to, had found a responsive audience among various groups of pathologists and physicians. The best illustration of this, perhaps, is to be found in a series of articles published in the *Journal of The American Medical Association* of June 3rd, 1916. The articles in question are the following: (1) "The Non-specific Factors in the Treatment of Disease," by Drs. James W. Jobling and William Petersen; (2) "The Treatment of Arthritis by the Intravenous Injection of Foreign Protein," by Drs. Joseph L. Miller and Frank B. Lusk; and (3) "The Value of Anaphylaxis in the Treatment of Gonorrheal Complications," by Dr. Louis B. Smith.

As showing the acceptance of the central thesis of the Proteomorphic Theory, Jobling and Petersen make the following clear statement: "Latterly the hematopoietic organs have come to be recognized as the chief source of antibodies. . . . . It would seem reasonable to suppose that any disturbance of the hematopoietic system might alter the antibody formation. . . . . In view of these facts, it would seem possible that the various agents act as a stimulant of hematopoietic tissue, which, as a consequence, suddenly floods the body with antibodies, thereby overcoming the infection. . . . . If this is the mechanism involved, it is important to keep in mind that the stimulus itself is not a specific factor, but that the hematopoietic system has been attuned to respond to a non-specific stimulus with the production of specific substances. Dunklin, working in this laboratory, finds that a marked increase in antibodies follows the intravenous injection of proteoses in immunized rabbits. In a general way this

Digitized by Google

mechanism of recovery would consist of a selective stimulation of the hematopoietic system by non-specific substances."

The "various agents" referred to as acting as stimuli to the hematopoietic tissue (or cytogenic tissue, as I prefer to call it), are sundry serums and vaccines, including a "non-bacterial proprotein split product—a deutero-albumose—used by Lüdke in the treatment of typhoid fever." "That such injections do not alter the disease process through supplying directly some deficiency, but rather through stimulating the elaboration of some substance before lacking, would seem to be the conclusion reached by recent workers. This would agree with the stimulating effects observed from injecting serum and whole blood subcutaneously in tuberculosis and pernicious anæmia (Esch, Busse, Weber)."

Following up the thesis, Jobling and Petersen make many interesting statements that invite quotation. While admitting the full value of specific immunology, they suggest that it has nevertheless, "resulted in the neglect of certain perfectly obvious lines of approach to medical problems." Referring to the striking results at times produced in a variety of infectious diseases by Schäfer's non-specific vaccine, "whether or not it was a safe remedial measure," they say: "The very fact that it did do certain things at times should have led to a study of why such favorable changes were brought about. The fact that it was palpably nonspecific, however, was sufficient to warrant the stamp of disapproval by the medical profession. It is only within the last two years that a certain definite movement away from this rather narrow point of view has occurred."

Again: "Schmidt is among those who have called attention to the fact that following vaccine therapy of any kind, the body becomes resistant to a variety of the commoner infections. So, too, it seems that during carcinoma and pregnancy (both, by the way, conditions distinguished by their high antiferment titer) a relatively low 'infection index,' as Schmidt terms it, is established. Von Wagner utilized a similar nonspecific method when he obtained favorable results in paretics treated with tuberculin; and only recently Blach has reported a series of cases of early syphilis treated with tuberculin."

Yet again: "Apart from the action of the vaccines, the protein split products, and the effect of both homologous and heterologous serums, observatins are recorded of the effect of milk injected intramuscularly (Schmidt), salt solution (Mitlander), dextrose solution, collodial metals, distilled water (animal experiments) and ferments (including the leucocytic extract of Hiss and Zinsser). It seems probable that the reaction and beneficial effects observed from these substances is based on a similar mechanism in all cases."

Digitized by Google

The "similar mechanism" in question, as already pointed out, is conceived to be the blood-forming apparatus.

All this, obviously, is directly in line with the Proteomorphic Theory, and with the idea of a comprehensive enzymic response to non-specific protein antigens, which furnished the main thesis of my paper of October 2, 1915. As further illustrating the principle, Jobling and Petersen give charts showing the effect of the intravenous injection of secondary proteoses in typhoid fever; and they emphasize the therapeutic value of the sharp febrile reaction that almost invariably follows the intravenous injection of the various non-specific antigens.

The paper on the treatment of arthritis by the intravenous injection of foreign proteins, by Miller and Lusk, appearing in the same number of the *Journal of the American Medical Association*, is in a sense supplementary to the paper just cited, inasmuch as the investigations were conducted with the proteose supplied by Drs. Jobling and Petersen.

"By giving from one to two c.c. of a 4 per cent. solution of this proteose," says the authors, "we obtained [in typhoid cases] the same result as with the typhoid vaccine, 20 per cent. of the treated cases terminating by crisis after a single injection. . . . . As stated, the proteose, in its chill, temperature reaction, leukocytosis, and percentage of cases in which the course of the disease was modified, gave the same results as the typhoid vaccine. These results are simply confirmatory of those already recorded, making it quite apparent that the sudden termination of the disease is not due to the specific character of the vaccine, but probably to the action of a foreign protein."

It was then decided to apply the method to another infection, and "we selected for this purpose acute, subacute, and chronic arthritis. . . . . Selecting, then, only those cases for study in which the disease was of a persistent type, we gave a 4 per cent. proteose solution, in doses of 2 c.c. intravenously. The patient reacted by a chill, rise in temperature, and moderate leukocytosis. The day following the injection there was a moderate but definite improvement in the joint symptoms.

"As our supply of proteose was limited, and as we believed that the reaction was due solely to the foreign protein, a typhoid vaccine was substituted for the proteose. . . . . The reaction was the same as when the vaccine was given to a typhoid patient except that the leukocytosis was much more marked, in two instances reaching 52,000. . . . . In three of our ten cases of acute articular rheumatism, immediately following a single intraveneous injection of 150,000,000, the fever terminated by crisis, the joint tenderness began to disappear, and within from twelve to twenty-four hours the joints were apparently normal. In these

Digitized by Google

three cases the results were permanent. All of the seven remaining patients were very much benefited following a single injection, but the results were either not permanent, or soreness still remained in some of the affected joints. Three or four injections, however, sufficed to relieve all symptoms. . . . . Results quite as satisfactory were obtained in six cases of subacute arthritis of from three to nine months' duration. These patients all received several injections. Here, as in the acute cases, great relief followed a single injection, and after three or four injections had been given, the patient could move his joints with comfort, could dispense with his cane, and in every way the results were most gratifying."

"Results even more striking were noted in cases of chronic gonorrheal arthritis of from two months' to three years' duration. . . . . That the reaction here and also in typhoid is a foreign protein, and not a specific protein, is probable."

Such results as these are obviously strikingly analogous to the results obtained at the Beebe-Williams Clinic in the treatment of rheumatoid arthritis with vegetable protein, as elsewhere reported.

The third paper already referred to in the *Journal of The American Medical Association* of June 3 by Dr. Louis D. Smith, gives further substantiation to the same thesis. Eleven cases of gonorrheal complications are cited. The results are noted of substituting normal horse serum for antigonococcic serum, and the conclusion is reached that there was no result obtained with the supposedly specific serum "which was not equally well effected with normal horse serum."

Of similar import are the conclusions of Dr. Abraham Sophian, of New York, as to the manner of action of serum used in the treatment of infantile paralysis recorded in the *Journal of The American Medical Association* of August 5, 1916. He reports success with the use of normal horse serum. He believes that the hyperleucocytosis induced by immune antimeningitis serum therapy is not specific, but, "to a very great extent a non-specific protein reaction." He suggests the use of normal human serum as desirable in treating infantile paralysis, avoiding the "sensitization" with horse serum.

Even more directly in line with the studies of the present monograph are the reports on the treatment of cancer with autolysates made by Klinger in Switzerland, as excerpted from the original publication and detailed in the *Journal of The American Medical Association* of November 4, 1916. Klinger explicitly postulates the stimulation of the blood-forming mechanism to the formation of cancer-destroying enzymes by autolyzed animal tissues.

All these studies, then, emphasize the suggestion that in considering serum therapy and vaccine therapy in their most specific

Digitized by Google

relations, we are always in touch with the broader general principle of non-specific protein therapy. It becomes at least an open question whether the good effects sometimes apparently attained by the use of bacterial vaccines as curative agents, may not be solely due to the protein element. This, of course, does not apply to the question of preventive inoculation with a specific vaccine. In that case, we are endeavoring to stimulate the production of specific antibodies to antagonize the toxins of a possible future invading army of bacteria of a given type.

But the most enthusiastic advocates of the vaccine method (and I count myself among them), have often felt that there is theoretical illogicality in using a vaccine for treatment of a patient whose body had already been invaded by the species of pathogenic bacterium from the bodies of which the vaccine is made. It has been impossible to present any sound physiological reason for adding more of a toxin to a system already poisoned by it.

It is at least a question, then, in the light of the observations just made, as to whether a protein free from the toxic principle in question would not produce all the beneficial effects of, let us say, the typhoid vaccine, without its deleterious effects.

Seemingly, in giving a vaccine to a patient already suffering from a bacterial invasion, we are benefiting and injuring with the same dosage; whether the net effect will be good or bad may depend upon a good many ulterior circumstances. Assuredly if all the good effects can be obtained while avoiding the bad effects, such a method is to be preferred. And it would appear that the use of non-toxic vegetable proteins offers such a possibility.

All of this is merely an elaboration of what I had in mind when, in my paper of October 2, 1915, I stated the explicit belief above quoted, that the extract of vegetable proteins "is a remedy against all protein infections"; and ventured the further prophecy that the demonstration of this principle constituted "the inauguration of a method that must in future rank with serum therapy and vaccine therapy—if, indeed, it does not altogether outstrip or totally supplant both these relatively new additions to the equipment of the practical physician."

I think it must be clear that the observations of the physicians I have just cited, as presented in the *Journal of The American Medical Association,* give new warrant to this prediction, and illustrate a wide acceptance of the non-specific protein principle that augurs well for the rapid extension of the method.

I have cited the above experiences of various observers not only because of their specific interest but because they constitute, in effect, corroborative testimony for the therapeutic value of the principles of protein reaction which it is the main purpose of the present monograph to exposit, the evidence for which is found

Digitized by Google

in our original researches at the Beebe-Williams Clinic, in connection with the reports of about 3,000 unpublished cases treated by 1,200 physicians in various parts of the world. Full details as to all of this will be given in the appropriate place; here I can only summarize the salient features of our investigation with brief reference to the precise character of the new protein antigens; their method of preparation; their applicability in the treatment of various disturbances of protein metabolism, including bacterial infections and the cancerous condition; and in particular the observed effect on the blood count, notably the differential leucocyte count, when the various proteins are administered hypodermically. Incidentally, I shall suggest a new classification of the protein antigens in general, and introduce the new word "Proteal" as a generic term descriptive of the vegetable proteins when administered hypodermically to serve as antigens stimulating the enzymic functions of the blood-forming apparatus.

New Protein Remedies

The development of the new series of medicinal proteins in the Beebe-Williams Laboratory came about as a result of the assumption, to which reference has already been made, that the observed action of the original extract above referred to was essentially due to its protein content. An analytical laboratory investigation had been made in which it was shown that each of the twelve constituents contributed a fractional quantity of protein to the extract; the major part of the protein, however, comes from the mustard seed, as might be expected.

It was at first contemplated to make clinical observations with each of the individual proteins, to determine whether any one of them or any particular combination of them had exceptional value in stimulating a characteristic physiological response of the organism. But since this, obviously, would involve an enormous expenditure of time and labor, it was thought that a short-cut might be effected by making the provisional assumption that any foreign protein of non-toxic character might produce an effective enzymic response. Theoretically, in the light of the Proteomorphic Theory, it should be so. We determined to find out whether it was so in practice.

Dr. Beebe and I accordingly set about to secure a series of extracts of vegetable proteins. A large variety of vegetable substances were used as the source of these extracts, among others alfalfa seed, alfalfa meal, hemp seed and rape seed. I mention these in particular because we are already in position to say something definite as to the therapeutic effects of these particular proteins. I may add, however, that the series of experiments now

Digitized by Google

under way contemplates the utilization of all the various food proteins.

The practical stimulus to the development of the new proteins was the fact that in a large number of cases patients suffering from inoperable cancer who had responded strikingly to the treatment with the original combination of vegetable proteins came finally to a seemingly static period, at which they showed notable improvement over their previous condition, yet now seemed no longer to respond actively to the stimulus of the remedy. Seemingly they were immunized against further enzymic response to the particular proteins in question But there seemed to be at least a possibility that they might take on fresh response if new proteins were administered.

This expectation was justified in a considerable number of cases to which the new proteins have been administered, singly or in combination, during recent months. It was found that patients who were virtually immunized to the combined proteins, taking large doses without tangible response, showed marked anaphylactic reaction when small doses of the new proteins were administered. Such being the case, it was not surprising that there should be a corresponding modification of clinical symptoms and a characteristic modification of the differential blood count to which I shall refer more in detail in a moment.

First, however, let me briefly describe the method of preparation of the new protein-antigens. It is exceedingly simple, and may be repeated by anyone having a fair knowledge of physiological chemistry, and an ordinary laboratory equipment.

The essential procedure consists of the extraction of the protein from the ground seed or other vegetable substance with a salt solution; precipitation of the protein from this solution with hydrochloric or acetic acid; washing with distilled water; and the re-dissolving of the relatively pure protein with sodium hydroxide. The final solution is standardized by testing for nitrogen, so that as ultimately used it contains two per cent. protein, this percentage, however, being modified in various experimental tests. The solution, being kept slightly alkaline, can be sterilized by heat after sealing the ampules in which it is placed for safe and convenient subsequent handling.

The proteins thus preserved will, of course, be quite inert if given by the mouth. Administered hypodermically in doses of from ten to sixty minims the effects are striking and characteristic. They include a certain amount of local erythema at the point of injection; a feeling of giddiness; nausea, malaise, rise of temperature, and a more or less pronounced chill.

These familiar anaphylactic symptoms vary in their intensity with different patients, and are not produced in the same degree

Digitized by Google

by different proteins. The protein of rape seed, for example, produces a much less severe general reaction than the protein of alfalfa seed.

If the subject to whom the protein extract is administered is, let us say, a patient with cancer of the uterus associated with pain, a fœtid discharge, and marked cachexia, there is likely to be a very notable modification of symptoms. The pain may largely disappear after two or three treatments; the character of the discharge may be so modified that it becomes watery and inodorous; and the general physical condition of the patient may be strikingly modified in a favorable direction. As the treatment continues, the neoplasm itself may undergo a conspicuous and unequivocal regression to a greater or less extent.

Similar modifications may be observed in malignant neoplasms of various types wherever located in the body. The reports of twelve hundred physicians dealing with more than 3,000 cases of inoperable cancer leave no question as to this. There remains, however, the highly interesting question as to how such changes are brought about by the hypodermic administration of small quantities of vegetable proteins. It is that question with which the present monograph is chiefly concerned.

MODIFICATIONS OF THE BLOOD-COUNT

A clue to the answer is found in the fact that conspicuous modifications of the blood count almost invariably follow the administration of the proteins. These changes are of a kind susceptible of interpretation in terms of the Proteomorphic Theory. But they have a high degree of interest quite aside from theoretical interpretations. As gauged by study of 150 hitherto unpublished cases, they appear to include a tendency to bring the polynuclear leucocytes and small lymphocytes towards the normal; whereas the basophiles and eosinophiles are markedly increased, and the large monocytes are increased by several hundred per cent.

Before giving details as to these interesting modifications of the blood count brought about by the administration of protein antigens, I would call attention to the highly interesting laboratory experiments recently reported by Drs. M. W. Manwaring and Yoshio Kusama, of the department of bacteriology and immunity of Leland Stanford, Jr., University, as recorded in the *Proceedings* of the Society for Experimental Biology and Medicine, of May 24, 1916. These experiments go to show that the blood corpuscles of a rabbit actively absorb goat serum protein, whether the goat serum is mixed with the (defibrinated) rabbit's blood in a receptacle outside the body or whether it is injected into the system of the living rabbit.

Digitized by Google

This observation, obviously, gives strong support to the assumption of the Proteomorphic Theory that the blood corpuscles are the chief agents concerned in dealing with foreign proteins—the assumption that forms the chief basis for the explanation of the therapeutic action of the protein remedies with which the present monograph is concerned.

In attempting to interpret the meaning of the observed changes in the blood picture, however, one is entering quite unexplored territory, and a territory in which the newly observed facts do not at all times serve as an accurate guide.

In point of fact, very little is definitely known as to the precise mutual relations of the different types of leucocytes. There is a general impression that these fall into two groups, one of myelytic origin and the other of lymphatic origin. In the former group, are the basophiles, the eosinophiles, the large mononuclears, and the neutrophiles. In the latter group, are the lymphocytes. Whether or not the lymphocytes should be divided into small and large, as two different classes, is a matter regarding which the authorities are not agreed. Also the question of the precise origin and functions of the large monocytes is by no means settled. Ehrlich regarded them as the forms which, developing through a transitional stage, became transmuted to polynuclears. But it does not appear that there is any positive evidence in substantiation of this view.

Furthermore, it has been disputed as to whether the large lymphocytes are the parent forms of which the small lymphocytes are the daughter cells; or whether, on the other hand, the small lymphocyte grows and develops into a large lymphocyte.

Meantime, it does not appear that anyone has given close study to the question as to the precise material out of which the bodies of the various leucocytes are developed, nor as to the specific distribution of their protein bodies after disintegration. It has been observed that there may be deviation of two thousand or three thousand leucocytes to the cubic millimeter under normal conditions in the course of a day. Reinart, for example, gives the average number of leucocytes at six o'clock in the morning as 5,125; and the average at 4 P. M. as 8,262. If we may accept such a variation as this as typical, it becomes obvious that the growth and disintegration of three thousand leucocytes to the cubic millimeter as a normal process during a period of twenty-four hours involves a cycle of protein metabolism that is highly significant. A very interesting question—and a question of great importance—arises as to whether the transmutation of raw materials, so to speak (with amino-acids for the ultimate building stones), through which the bodies of the leucocytes are built up takes place only in the mother organs of bone marrow and lymph nodes, or

Digitized by Google

whether the free leucocytes in the blood stream continue to grow and develop, taking to themselves food pabulum, and passing through stages of individual development that may be properly spoken of as juvinility, maturity, and old age.

The well known fact that the larger types of leucocytes exercise a phagocytic function, seeming to feed on the bodies of bacteria, gives strong support to the supposition that these cells are capable of ingesting protein pabulum and converting it into material for the increment of their own particular protein substance. It is believed by some observers that the granular structure of the leucocytes commonly spoken of as myelocytic (that is to say, of bone-marrow origin) represents something comparable to a glandular substance, constituting a secreting mechanism. The secretions in question are supposed to be enzymic in character, representing the various anti-bodies, in particular the so-called complement.

According to one view, the granular leucocytes are all of bone-marrow origin, and constitute a class apart. But this view is obviously inconsistent with Ehrlich's claim that the large non-granular mononuclear leucocytes develop individually into neutrophiles.

Evidence in the matter is by no means as conclusive as could be desired, yet it is universally admitted that different organs of the body may on occasion take on the function of leucocyte-production; and it may very well be questioned whether there is any such distinct and fundamental difference between the blood-forming cells of the bone marrow and the similar cells of the lymphatic system as has sometimes been suggested. It may fairly be assumed, however, on embryological grounds that the lymphatic system constitutes a somewhat more primordial structure than the bone marrow inasmuch as the latter is a relatively late development in the fœtus. But, on the other hand, many observers are disposed to trace the origin of the primitive forms of cells that appear in the blood under certain abnormal conditions (notably the leukæmias) to the bone marrow rather than to the lymphatic system.

It is more than likely that, when the systemic disturbance is sufficiently profound, both sets of organs may revert to a somewhat primordial manner of functioning, and put out cells of a more embryonic type than the ones usually sent into circulation. Interesting hints as to the mutual relations of the various types of white corpuscles are given by charts in which the different groups of cells are represented by graphic lines. It is hoped that the study of these in connection with the protein remedies will throw new light on the obscure relations of the different types of leucocytes. When a much larger series of charts is available than at present,

Digitized by Google

it is certainly to be expected that relations will be observed between the mutual rise and fall of the different types of corpuscles under treatment that will help to explain the genetic relations of these bodies.

In making such charts, it is desirable to transform percentages of the differential leucocyte count to actual numbers. When this is done, one is impressed with the general observation that there seems a strong tendency, under the proteal treatment, for the polynuclear leucocytes and the small lymphocytes to be modified in number so that, after treatment has been continued for a time, they fall within normal limits. Here, for example, is one chart (Case No. 332) in which at the outset the number of neutrophiles was 5,680, and the number of small lymphocytes 2,131; these numbers representing in each case an excess above the maximum normal limits, as usually computed. But after treatment had extended over about 90 days, it was observed that the polynuclears numbered 4,356, and the small lymphocytes 1,824; both these numbers representing a (high) normal count.

But in the meantime, it should be noted that the large monocytes, which at the outset numbered 1,420 had increased to 2,403. The original count is far in excess of the normal (which seldom exceeds 400), and the final count exceeds the maximum normal limits by 600 per cent. The assumption is, according to the present thesis, that before treatment the large monocytes had been stimulated to excessive production under influence of the disintegrated cancer cells; and that the protein treatment effected a further stimulation.

A similar proportionate increase in the eosinophiles has taken place, there being none noted at all before treatment and the number having risen almost continuously until 356 were noted at the later count,—about double the normal maximum limit.

Whatever the interpretation put upon these facts, it would appear, as already pointed out, that such a super-normal count of large monocytes and eosinophiles constitutes a favorable condition in the organism associated with improved general health of the patient and a tendency to combat the cancer cells effectively.

Another chart illustrates the same principle in a different way; inasmuch as it was necessary to increase the number of neutrophiles in order to bring them to a high normal limit. It will be observed in this chart (Case No. 369) that at the outset the neutrophiles numbered 3,370 and the small lymphocytes 2,630. At the end of three week's treatment, the polynuclears had risen to 4,935, and the small lymphocytes had dropped to 1,410. Here, as before, the final count shows polynuclears and small lymphocytes within normal limits.

Digitized by Google

In the meantime, in this second chart, as in the first, the large monocytes have risen conspicuously; in this case from 1,150 to 2,608; and the eosinophiles have increased from 213 to 329. The numbers here are substantially in accord with those shown in the other chart. Such close agreement is a matter of coincidence, although the same general principle will be seen reiterated in a large number of cases.

A striking feature of both these charts is the marked modification in the number of neutrophiles and small lymphocytes from the initial dose of the vegetable protein. A question not unnaturally arises as to whether there is any mutual relation between the two groups of leucocytes, or whether the modification of their numbers has been brought about independently. Glancing at the first chart, one might think that there must be some mutual relation, inasmuch as the lines showing modification of the neutrophiles run almost parallel with those showing modification of the small lymphocytes. But in the second chart, we find that the slope of the line is reversed, the neutrophiles showing a rapid rise after the first dose and the lymphocytes a rapid decline.

It is not impossible to frame a theory that would harmonize these seemingly contradictory results, but perhaps it is not worth while to attempt to do so at the moment. Our chief present concern is with the observed facts, which fortunately are unequivocal. As above outlined, these include a notable departure from the normal blood picture brought about by the administration of the protein remedies as evidenced in a relatively enormous increase of the larger monocytes, a conspicuous increase of the eosinophiles and basophiles; and a tendency to bring the small lymphocytes and the neutrophiles within normal bounds.

By way of recapitulation, it is well to recall that Vaughan's experiment seems to show that the specific enzymes of the large mononuclears have particular value in proteolyzing the cancer proteins. Stated otherwise, the large mononuclears would seem to have particular affinity for cancer proteins; which is only another way of saying, probably, that they are particularly adapted to deal with proteins of an embryonic type. The fact that the large mononuclears abound relatively in the normal blood of the child may be recalled in this connection.

Relative Non-Toxicity of the Proteals

From the standpoint of practical therapeutics, the other consideration that I would emphasize here is the thought that the proteins introduced hypodermically may serve not merely as stimuli to the blood-forming organs, but as actual pabulum for feeding the leucocytes that make up the chief company of these bodily defenders. This supposition would explain the clinical benefits

Digitized by Google

observed from the use of large doses. Conceivably, also, it may explain the benefits derived from shifting the treatment from one protein to another. Perhaps it is not too fanciful to suggest that the lymphocyte may turn with avidity to a new protein after its appetite for an older form has become jaded.

In any event, the fact that the patient frequently increases in weight, as well as in general health, under the protein treatment suggests that the action of the protein introduced parenterally is not altogether destructive. In one way or another, apparently, it may ultimately be assimilated in such a form as to be of value to the normal body tissue. This, however, must represent but a minor share of its influence, as the total quantity of protein thus introduced is small. The main influence must be an indirect one; yet this influence may very well be effected through supplying directly to the leucocytes material from which to develop their enzymes. The ultimate distribution of the residual portions of the injected proteins, with the aid of the red corpuscles, as exposited in the Proteomorphic Theory, is familiar to the present reader.

So long as we consider the treatment of inoperable cancer cases only, the question of the toxicity of the vegetable proteins, when administered for long periods of time, is not very important; inasmuch as the condition of the inoperable cancer patient is confessedly desperate in any case. But when we come to consider the use of the proteals in connection with other maladies, for example, rheumatism, the case is obviously different. It now becomes highly important to inquire whether there are consequences incident to the administration of large doses of proteals, or doses for a continued period, that militate against such administration.

The experiments of Dr. Van Alstyne in the administration of proteins to dogs are highly intersting in this connection. The experimenter found that very small doses of bacterial toxins, including Coley's Fluid, brought about a condition of toxicity, with notable cachexia, in the dog, that made it impossible to continue the administration for a considerable length of time without disastrous consequences. But on the other hand, she was able to administer the vegetable protein edestin in large doses without producing unpleasant symptoms of any kind, beyond a temporary slight chill and rise of temperature. Edestin was administered in a concentrated solution, and in doses of fifteen to twenty cubic centimeters.

This laboratory observation is obviously in accord with the observations of the physicians who have administered mixed proteals to patients for long periods of time; and who have observed, in the vast majority of instances, a marked improvement in general health, and the disappearance rather than the onset of cachexia.

Digitized by Google

In this connection it will be of interest to note the blood conditions, as well as the clinical condition, of a series of cases still under observation at the Beebe-Williams Clinic who have been under fairly continuous proteal treatment for periods of from one year to a year and a half, as elsewhere recorded in this volume.

Other Remedial Uses of the Proteals

It remains to give brief consideration to sundry conditions of the organism not characterized by the presence of malignant neoplasms, but associated with organic maladjustments that make possible the development of such neoplasms; and directly characterized by proliferation of protoplasmic tissues in my judgment comparable with cancer proper,—though not commonly viewed in this light by physiologists or pathologists.

I have in mind various conditions characterized by disturbances of nutrition and assimilation that lead to abnormal growth of cells in one region or another of the body, all evidencing conditions of hyperplasia that had certain elements of "malignancy" inasmuch as they are deleterious to the organism, though varying enormously in the degree of their obnoxiousness. Among these conditions are: (1) Anæmic obesity, in which lawless adipose cells encroach on more useful tissues; (2) pernicious anæmia and the lymphæmias and myelæmias, characterized by hyperplasia of the blood-forming tissues; (3) glandular hypertrophy, as in goitre, thymus enlargement, and splenomegaly; (4) rheumatoid arthritis, characterized by hyperplasia of tissues associated with joints; (5) general arterio-schlerosis, characterized by hyperplasia of the tissues of the arterial walls; (6) sundry lipomas and fibromas of "benign" character; in addition to (7) the neoplasms commonly recognized as "malignant."

I venture to associate all these conditions, and to trace them to a common origin in maladjustments of protein metabolism, and I suggest that it might not be illogical to group them all under some such generic title as hyperproteomorphism, or the cancerous condition. I shall not attempt here to discuss even in briefest detail the interesting questions in pathology that arise in connection with the implied association of conditions of such seeming diversity. Such a discussion will form the basis of another book. Here I wish to point out very briefly two or three sets of clinical facts that give at least a measure of support to the unorthodox conception applied in this classification.

I would first call attention to the familiar fact that a well known type of fatty and mucinous hypertrophy known as myxœdema, is associated with perversions of the thyroid function; and the further fact that there is believed to be a close asso-

Digitized by Google

ciation between the integrity of the hormone functioning and bodily metabolism in general.

Without attempting to point out except in this general way what I conceive to be the bearing of the observation, I wish to note that it has been observed by at least one physician who was administering the mixed proteals in a case of cancer that an enlarged thyroid disappeared during the treatment. Here is the letter in which the case is reported:

"Kindly advise me as to the use of Autolysin in goitre. Have noticed in one case treated for sarcoma the patient had a marked parenchymatous goitre, which has entirely disappeared under treatment. Has anyone else so reported and do you know if treatment has been tried in cases of cystic or parenchymatous goitre, if so with what result and how long under treatment?"

In this case the remedy had not been given with any thought of effecting the thyroid; but Dr. Beebe has used vegetable protein in connection with his thyroid anti-serum in the treatment of a number of cases of goitre, seemingly with rather striking results. Observations along this line, however, have not yet reached the point of readiness for detailed publication. By way of anticipation, however, we may note that the modification of blood count under influence of the thyroid serum is singularly like that brought about by the proteals; suggesting that the action of the serum is partly explicable on the basis of its protein content. Doubtless there is also an anti-thyroid enzyme element, but the agent that causes decrease in size of the enlarged thyroid is probably not this anti-ferment but the sheep-serum protein.

In the next instance I would note that in a case of cancer under mixed vegetable protein treatment in Dr. Beebe's hands, there existed the complication of severe rheumatoid arthritis. The latter condition cleared up entirely—a seeming cure being effected under the protein treatment. This observation led to the administration of the proteals in several cases of rheumatoid arthritis uncomplicated by the presence of cancer; and the results of such treatment have been highly gratifying. In a recent case, the response to rape seed protein by itself seemed as active as the response to the combined proteins.

As regards the relation of the new treatment to the form of nutritional maladjustment manifesting itself in pernicious anæmia, I cannot do better than to quote a letter received not long ago from a physician in Michigan, which is self-explanatory.

"I have been using Autolysin in a late stage of pernicious anæmia on purely theoretical grounds. After ten injections have found an increase of over 15 per cent. in the red cells with an accompanying favorable alteration in the differential leucocyte count, and have noted nucleated red cells for the first time since the treatment was begun.

Digitized by Google

"The patient, a man over 50 years of age, carpenter by trade, is without means, having been unable to work for over 18 months. I ordered the remedy for him on my own responsibility, having become familiar with the product and its literature through using it in a supposedly hopeless case of carcinoma of the liver, secondary to gall bladder carcinoma in my wife's mother. Gall bladder and neighboring involved liver were removed and reported by pathologist at University of Michigan as carcinoma, and a hopeless prognosis given.

"Having read Dr. Beebe's article, I secured a supply of Autolysin from Dr. V. C. Vaughan, Jr., of Detroit, and continued treatment between 3 and 4 months. The patient is in better flesh than ever before, is well and comfortable in every way, and the right lobe of liver which is low, feels perfectly smooth and healthy."

It will be observed that this letter has double interest, inasmuch as it bears on the question of the value of combined proteins in the treatment of a "supposedly hopeless case of carcinoma of the liver," as well as on the question of its value in the treatment of pernicious anæmia. It is, however, only the latter point that is at the moment pertinent. I shall not elaborate the point, however, beyond stating that a letter from the same physician received several weeks later confirms the observation that the condition of this patient is benefited by the autolysin treatment. Obviously this is no more than might be expected of the administration of a remedy which has been observed in a very large number of cases to produce striking and beneficial modifications of the blood count.

A further report on the progress of this case comes to hand in a still more recent letter bearing date of October 19, 1916, telling of the resumption of the Autolysin treatment after a considerable intermission.

"The pernicious anaemia case has shown a remarkable change for the better since using last package of ampules. This patient, a county case, was in a somnolent condition, and in fact had been removed from ward to private room to die. He is now bright, has lost all the general oedema, eats well, and wishes to be up and around."

Just as the physician above quoted was led "on theoretical grounds," following his observations of the results of the proteal treatment, to inquire whether the remedy might not be of value in connection with pernicious anæmia, other physicians have questioned whether its capacity to stimulate the production of corpuscular enzymes and to bring up the blood count might not make it of value in the treatment of bacterial diseases.

Very brief but specific reference to such a possibility was, indeed, made in my paper of October 2nd, in the *New York Medical Journal*. It would not accord with the scope of the present

Digitized by Google

monograph to discuss the matter here. I may be permitted, however, to state that a limited experience in the treatment of tuberculosis with combined vegetable proteins appears to warrant the hope that non-toxic vegetable proteins will prove available to fortify the defensive mechanism of the body (according to the present thesis) by stimulating the corpuscular activities against the

TABLE I.—ORIGINAL CASES AT THE BEEBE-WILLIAMS CLINIC

48 UNSELECTED CASES AFTER AN AVERAGE PERIOD OF 102 DAYS OF PROTEIN TREATMENT.

Case No.	Name	Nature of Case	No. of Days	Hemoglobin	Red Blood Corpuscles	White Blood Corpuscles	Polynuclears	Mononuclears		Eosinophiles	Basophiles
								Large	Small		
106	Miss A...	Thyroid	195	100	5,376,000	8,000	61.5	20	15	3.5	0
311	Mrs. A...	Thyroid	4	90	5,250,000		56.5	19	22.5	2	0
	Miss A...	Thyroid		100	4,480,000	6,700	58	13.5	23	4.5	1
271	Mrs. B...	Sarcoma	16	65	3,328,000	10,250	79.3	8.3	10.6	1.6	0
223	Mrs. B...	C. of Uterus	69	85	4,064,000		80.6	10.6	8.6	.6	0
	Mr. B...	Tuberculosis	40	90	5,600,000	8,400	45.5	35	10	4	.5
	Fr. B...	Diabetes		95	5,296,000	8,100	55.6	20	20.3	3.3	.6
135	Mrs. B...	Carci. of Breast	84				67	16	16	1	0
133	Miss D...	Thyroid	184	100	5,632,000	6,400	55.5	24.5	18.5	1.5	0
167	Mrs. D...	Carci. of Breast	73	85	4,370,000		66	18	14	2	0
8	Miss D...	Thyroid	205	90	4,082,000	6,500	43	24.5	29	3.5	0
192	Mrs. D...	Carci. of Breast	18	85		9,620	64.3	15	17.3	3.3	0
353	Miss E...	Thyroid	59	90	4,640,000	7,300	58.5	24	16.5	1	0
305	Mrs. E...	Carci. of Breast	15	80	2,848,000		77.6	13.6	5	3.6	0
88	Miss F...	Thyroid	211	100	5,440,000	8,000	60	20	18.5	.5	0
209	Mr. F...	Ep. of Tongue	150	100	5,600,000	7,700	70	14.5	13	2	.5
186	Mrs. G...	Thyroid	90	85	3,976,000	9,340	57	8.3	33.3	.3	0
261	Mrs. G...	C. of Uterus	52	85	5,000,000		72	11.6	12.6	3.6	0
250	Mrs. H...	Thyroid	144	95	4,032,000	7,200	47.5	24	25	2.5	0
	Mrs. H...	C. of Intestine		80	4,032,000	11,300	67	13	18	1	1
221	Mr. H...	C. of Œsophagus	65		5,320,000		74	13.3	11.6	1	0
	Miss K...	Thyroid		90	4,490,000	7,220	62	23	13	2	0
395	Mr. K...	Indigestion	61	100	5,440,000	7,100	62.5	14	18.5	5	0
307	Mrs. K...	C. of Uterus	63	75	3,840,000		68	11	20.5	.5	0
48	Mrs. L...	Thyroid	114		5,296,000	5,720	50	15	35	0	0
326	Miss L...	Thyroid	75	100	4,928,000	6,600	62	22.5	14.5	1	0
207	Mrs. L...	Int. Toxæmia	96	90	4,040,000	8,300	52	15.6	24.6	7.6	0
372	MissMcG	Thyroid	98	100	4,576,000	9,200	55	20	16.5	8	.5
40	Mrs. M...	Thyroid	201	95	4,524,000	7,100	49	19.5	26	5.5	0
165	Sr. M...	C. of Breast	101	100	4,960,000	6,300	52.5	21.5	24.5	1.5	0
264	Mr. N...	" " Œsophagus	351	75	4,028,000		59.6	20	9.3	1	0
283	Mrs. Q...	" " Breast	84	90	4,784,000		62	23	14	1	0
259	Mr. R...	Toxaemia	137	100	5,308,000	6,400	77	14	7.5	1	.5
268	Mrs. S...	Endoth. of Throat	52	95			62.5	24	12.5	1	0
274	Mrs. S...	Carci. of Uterus	38	70	3,400,000		84	4	8.6	2.6	.6
281	Mr. S...	Sarc. Testicle	42	70	2,168,000		68.5	11.5	14	6	0
298	Mrs. S...	Carci. of Breast	19	80	3,856,000		70	11.6	10	2.6	0
43	Mrs. S...	Thyroid	131	84	4,160,000	7,930	62	12	26	0	0
24	Mrs. S...	Carci. of Breast	113	90	5,450,000	7,800	64	14	21	1	0
208	Mrs. T...	Thyroid	98	90	4,496,000	8,330	61.25	15.5	18	3.75	1.5
159	Mr. V...	C. Mediastinum	75		4,620,000		78.5	15	6	.5	0
407	Mr. W...		60	100	5,664,000	7,000	77	9	13	1	0
25	Mr. W...	Thyroid	215	100	5,728,000	9,000	68	15	16.5	0.5	0
32	Miss W...	Thyroid	220	95	4,250,000	7,600	73	11	15	1	0
47	Mr. W...	C. of Tongue	119	80	3,440,000	10,250	77.6	13.3	6.3	2.6	0
247	Mrs. Wn	C. of Breast	62	65	3,804,000		63.5	15.5	18.0	2.	0
382	Mr. Wk...	Exophthalmus	60	95	5,324,000	7,500	44.3	30.3	23.5	2.3	0
44	Mrs. D...	Rheumatoid Arthritis	196	95	4,444,000	6,700	54	25	16.5	4.5	0
	Average		102	89	4,673,000	7,830	63.4	16.9	16.8	2.33	.1

tubercle bacillus. If a non-specific protein can produce this effect, there would seem to be no reason why the same protein, or allied proteins, may not give effective aid in combating all types of pathogenic bacteria.

Digitized by Google

Theoretically, the hypodermic injection of non-toxic vegetable proteins (if the present thesis is correct) should prove a sheet anchor in the treatment of all infectious diseases characterized by the entrance of pathogenic bacteria into the parenteral system.

On occasion it may be desirable to combine the proteal with a specific vaccine.

Now for the first time remedies of this character are available, and we may expect that the matter will soon be put to elaborate tests.

There are many open questions in connection with the protein treatment that I shall not refer to here in detail. The question whether the protein introduced had best be full-sized molecule, or a modification in the form of a proteose, or peptone, or even a combination of polypeptids; the question whether vegetable and animal proteins may advantageously be combined or used alternately; and various allied problems are having careful consideration but cannot hope for final answer except after a long term of observation on the part of many workers.

A Proposed New Classification of Protein Antigens

Meantime it would appear that the experience already at hand puts us in a position to round out the classification of protein remedies in a manner comprehensive and fairly satisfactory. To that end, I suggest the following:

It would be convenient to have a generic term connoting remedies involving the use of proteins that are introduced hypodermically and thus act as antigens.

I suggest the new word *Proteantigens* as such a generic term; the short definition of a proteantigen being: A hypodermic antigen containing protein. As an alternative, the word *Macrocytosins* might be used,—suggested, obviously, by the observed power of the protein antigen to stimulate the production of the large mononuclear leucocytes, or macrocytes.

I further suggest the following classification of Proteantigens or Macrocytosins:

(1) Animal Proteantigens, or Serums and Autolysates, of which typical examples are Beebe's anti-thyroid serum, his human thyroid extract, and the non-specific serums of animals wherever used therapeutically, as in case of horse serum to stop hemorrhage, and the autolysates of Fichera.

(2) Mixed Proteantigens, or Viruses (developed in the system of an animal inoculated with bacterial proteins), of which typical examples are Behring's diphtheria anti-toxins; tetanus anti-toxin; and Jennerian vaccine.

(3) Bacterial Proteantigens, or Vaccines; of which Wright's anti-typhoid vaccine is the type.

Digitized by Google

(4) Vegetable Proteantigens, or Proteals, of which the only ones extensively tested are (1) the hay-fever "vaccines" prepared from the pollen of plants; (2) the Horovitz-Beebe combined protein extract (Autolysin); and (3) the various vegetable proteins used at the Beebe-Williams Clinic in our recent experimental and practical investigations.

Knowing how loath the profession is to accept dictation in matters of terminology, I suggest the above classification in all diffidence. A somewhat more general classification suggests itself in the division of all Proteantigens into: (1) Specific Proteantigens, including most of the serums, viruses, and vaccines (excluding, however, the plain serums); and (2) Non-specific Proteantigens, of which the chief examples are the deutero-albumose of Lüdke, the Horovitz-Beebe extract, and the Beebe-Williams proteals.

Let me repeat that I suggest these classifications only tentatively, and because they seem to me to have an element of convenience. Certainly we need a generic term to describe the vegetable protein antigens of which the original Horovitz-Beebe extract is the type; and the word *proteals* has the merit of being short, easily pronounceable, and suggestive. It may be thought that, etymologically, the word *proteils* would be more appropriate; and it has been suggested that "proteals" would indicate a derivation from "protean" rather than "protein"; but this criticism, though perhaps valid, is scarcely an objection, inasmuch as the general character (non-specific) of the response evoked by the vegetable antigens suggests a range of activity that may perhaps not unjustly be described as protean.

A more detailed presentation of this aspect of the subject will be given in another connection. Meantime, I repeat, that the word proteal appears to me to be a peculiarly appropriate one for these new remedies. In any event, it has the merit of convenience. It remains for the profession to decide whether this name, or some quite different one, shall be accepted as the familiar designation of vegetable proteantigens, or macrocytosins, in general.

By Way of Summary

In conclusion, then, let me repeat: Proteantigens in my opinion, are not specific antagonists of the cancer cell. They are antagonists of the misplaced protein molecule of whatever character. They may be used as logically in the treatment of tuberculosis, typhoid fever, and other bacterial diseases, as in the treatment of cancer.

They should be of service in disturbances of protein metabolism of every type; in goitre, arterio-schlerosis, and rheumatoid

Digitized by Google

arthritis, not less than in combating every type of malignant neoplasm. They are indicated in pernicious anaemia (and the various leukaemias) however superinduced.

The principle of the use of non-toxic proteins as antigens in dealing with all foreign protein invasions and malignant growths would appear to be one of the most comprehensive curative principles known to present day therapeutics. It is a logical extension of the principles of serum therapy and vaccine therapy, and its introduction probably marks the beginning of a new era in preventive and curative medicine. The method is only at its beginnings. Much is to be learned as to the varied effect of different proteins and protein products; the best methods of extraction and preparation; and the most effective methods of administration. But it must always be remembered that the method, as a distinctly recognized therapeutic entity, had its origination and gained its first impulse from the practical experience of the profession with the original proteal extract (Autolysin Horovitz-Beebe) in the treatment of inoperable cancer.

That is why I venture to suggest that the method, in its wider implications, may not inappropriately be spoken of as illustrating and utilizing the "Autolysin Principle." In a still more comprehensive sense, it might be said to represent the "Proteomorphic Principle."

TABLE II.—ORIGINAL CASES AT THE BEEBE-WILLIAMS CLINIC

BLOOD COUNT IN CASE NUMBER 294—CARCINOMA OF THROAT

Number of Days Treated	Hæmoglobin	Red Blood Corpuscles	White Blood Corpuscles	Polynuclears	Mononuclears		Eosinophiles	Basophiles
					Large	Small		
42.....	95	4,864,000	7,300	74.6	7.3	18	0	0
45.....	90	4,944,000	8,850	81	4	13.3	1.6	0
46.....	85	5,000,720	8,320	69.6	12.6	17	.6	0
	85	4,528,000	8,660	81.3	12.6	6	0	0
47.....	85	4,690,000	8,880	63.2	21.75	14	.75	0
48.....	85	4,400,000	8,770	60	26	13	1	0
50.....	85–90	4,728,000	8,890	65	20	14	1	0
51.....	90	4,902,000	9,220	55	26.3	26.3	1.6	0
53.....	90	4,880,000	9,110	65	20.25	12.5	2.25	0
54.....	90	4,480,000	9,150	67.3	19.3	10.3	0	0
55.....	90	4,472,000	9,220	70.6	18	8.3	3	0
56.....	90	4,504,000	9,550	75	16.3	5.6	2.6	.5
57.....	90	4,550,000	9,220	65	20.6	12	2.3	0
	90	4,864,000	9,330	67.25	21.5	8.25	2.25	.75
60.....	95	4,912,000	9,110	66	21.5	9.75	2.5	.25
	95	5,088,000	9,000	64.25	17.25	15.75	2.75	0
62.....	95	5,256,000	9,100	67.5	20.5	9.25	2.5	.25
63.....	95	4,952,000	8,500	60.5	21	14.25	4	.25
64.....	95	4,776,000	8,220	61.25	27	8.5	3	.25
65.....	95	4,728,000	8,440	63.3	23	9.3	5.3	.3
66.....	95	4,568,000	8,440	72.6	18.3	4.6	4.3	0
69.....	95	5,002,000	8,880	69.3	19.6	10	1	0
70.....	95	5,000,000	8,660	69	18.3	9.3	3.3	0
73.....	90–95	4,632,000	8,660	68.5	17.25	11.75	2	.5
75.....	90–95	4,400,000	8,550	69.5	17.25	10.75	2.5	0
76.....	95–100	4,440,000	9,000	68	18.3	10	2	.6
77.....	95–100	4,816,000	8,000	63.3	21	13	2.6	0

Digitized by Google

PART II

CANCER: INTERPRETED IN THE LIGHT OF THE PROTEOMORPHIC THEORY AND THE AUTOLYSIN PRINCIPLE

SECTION I

THE NATURE OF CANCER

In the paper of October 2, 1915, in the *New York Medical Journal,* I suggested the following definition and interpretation of cancer:

One might define cancer, in the light of the present theory, as a systemic condition characterized by the development of neoplastic cells of a somewhat embryonic type, in conjunction with an excess of leucocytes in the blood and a deficiency [actual or relative] of red blood corpuscles.

It must further be postulated that the neoplastic cells are of a type susceptible to the attacks of leucocytic enzymes, so that there is a constant tendency to disintegration of some of these cells under the attacks of the white blood corpuscles. Meanwhile, the deficiency [actual or relative] in red blood corpuscles makes it impossible for the system to deal adequately with the partially hydrolyzed protein products resulting from the breaking down of some of the new cells under the attacks of the leucocytes. The net result is a condition of protein poisoning or autointoxication which, when fully developed, constitutes the characteristic "cancer cachexia," and ultimately causes the death of the patient.

It should be observed that this new definition of cancer explains the hitherto obscure fact that almost any kind of new growth in the organism may on occasion take on the characteristics of malignancy. A fibroid tumor of the uterus, for example, is not ordinarily "malignant" because its tissues are of a type that the leucocytic enzymes cannot readily attack—largely, perhaps, because of their slow development and firmness of texture. Yet on occasion, as is well known, portions of a fibrous growth may become susceptible to disintegration under the attacks of the bodily enzymes; and in such a case, should the red blood corpuscles fail of their appointed task, a condition of veritable malignancy is attained, and the aforetime fibroid becomes a cancer.

Ordinarily, however, the neoplastic growth is from the outset composed of such cells as are more or less susceptible to the

Digitized by Google

action of the leucocytes; and, from a pathological standpoint, it is permissible to regard all such growths as nascent cancers. In a vast majority of cases, however, the neoplasm is denied opportunity of considerable growth, because of the immediate attacks of the leucocytes, which are backed up by the erythrocytes to such good effect that the neoplastic proteins are completely dissociated and eliminated from the body without producing harmful results, and, indeed, as a rule, without being given any consideration whatever.

It is probable that there are scores of nascent neoplasms that are dissociated and obliterated for every one that attains mastery over the corpuscular bodily defenders and becomes a tangible neoplasm. It is probable, in other words, that every insignificant lesion of the bodily tissues that calls for the development of new cells in the process of repair, might be regarded as an incipient malignant neoplasm; and is prevented from becoming an actual menace only by the efficient activities of the corpuscles that are normally present in adequate numbers for the bodily defense.

In elaboration of the idea underlying this conception of cancer, I now suggest the following expanded definition:

Hyperproteomorphism, or the Cancerous Condition, is a systemic condition characterized by a profound disturbance of protein metabolism involving originally the blood and blood-forming mechanism; evidenced by disturbances of the corpuscular balance and the abnormal proliferation of cells of one type or another; frequently, *but not necessarily,* associated sequentially with local neoplasms comprising cells that are partly subject to hydrolysis under influence of the enzymes developed by the white and red corpuscles.

As elaborating the definition, I suggest the following classification of the varied manifestations of the cancerous condition:

(1) Lymphatic and Myelogenous Leukæmias and Pernicious Anæmia, where the hyperplasia involves the blood-forming tissues.

(2) Anæmic obesity, characterized by excessive fat-foundation and deposit, at the expense of more useful tissues.

(3) Proteoid hypertrophy, as in Grave's Disease and myxoedema, where the lawless new growth involves glandular and lymphatic tissues.

(4) Chronic rheumatoid arthritis, where the maladjustment of metabolism manifests itself in a tendency to new growths in connection with the cartilage of the joints.

(5) Arterio-schlerosis, where the localized evidence of nutritional maladjustment involves the tissues of the circulatory apparatus.

(6) Benign neoplasms, where a local irritation in association with the disturbance of protein metabolism has led to a prolifer-

Digitized by Google

ation of localized tissues not freely subject to proteolysis by the corpuscular enzymes.

(7) Malignant neoplasms, or true cancer, where a localized irritation or abrasion has cooperated with protein maladjustments to cause a proliferation of epithelial, endothelial, or connective tissues constituting a more or less conspicuous neoplasm the tissues of which are to some extent subject to hydrolysis by the corpuscular enzymes. Here the development of the neoplasm in itself evidences the disturbed conditions of protein metabolism in the body (deficiency of corpuscular enzymes), and the new cells tend further to disturb that maladjustment by presenting additional protein material for hydrolysis.

I am fully cognizant that so revolutionary a definition and classification as the above, in which it is suggested that the cancerous condition is not necessarily associated with the presence of such a neoplasm as is commonly supposed to constitute the essentials of the disease, must excite surprise and opposition. But I venture to believe that the more closely the matter is considered, the more valid will seem the reasoning on which the interpretation is based. It will appear presently that there is also an important body of clinical evidence that gives support to the view above presented.

SECTION II

THE ORIGIN OF CANCER

What I have to suggest as to the origin of cancer follows as a matter of course from the theory just outlined as to the nature of the disease.

Whatever tends to disturb protein metabolism in the body may be considered as a predisposing cause of the malady. Familiar causes of such disturbance are (1) lack of exercise, (2) excess of protein food, particularly of animal proteins, (3) inadequacy of the protein intake.

It is obvious that the second and third of these causes of protein maladjustments are mutually exclusive. They must both be borne in mind. An excess of proteins in the diet, resulting in a putrefactive mass in the bowels and the entrance of a certain amount of unbroken protein into the parenteral system may overwhelm the blood corpuscles and produce an anæmic condition comparable to that due to a lack of adequate protein for the building up of fresh supplies of blood corpuscles.

It will be recalled, of course, that there is constant destruction of the red corpuscles in the spleen and liver, through which

Digitized by Google

(according to the proteomorphic theory) byproducts of protein metabolism that are toxic in character are excluded from the system. To compensate this destruction, there must be a constant building of new corpuscles, implying fresh protein supplies and an enormous aggregate expenditure of energy. If the necessary protein supplies are brought in excessive quantities, it follows that the red corpuscles have an excess of byproducts (of the polypeptid order) to deal with and are necessarily destroyed in excessive numbers. To keep up the supply, calls for an increased expenditure of energy, putting a needless tax on the bodily machine that may manifest itself in an abnormal blood count, increased blood pressure, and ultimately in one or another of the conditions of localized maladjustment above listed.

But it does not by any manner of means follow that the only cause that can produce such maladjustments is an excess of protein in the digestive tracts. It has already been implied that a marked deficiency might lead to a corresponding sequence of events. The presence of large numbers of bacteria in the intestinal tract is in itself a factor that makes constant work for the red blood corpuscles, resulting in a steady nitrogen loss and necessitating a constant restocking with nutritive proteins. So protein starvation might be quite as disastrous as protein repletion. The happy mean, here as elsewhere, constitutes the road to health.

As to exercise, a somewhat similar line of reasoning applies. Every physician nowadays recognizes the necessity for a certain amount of exercise in normalizing the processes of metabolism. But it must not be overlooked that excessive exercise, carried to the point of exhaustion, may have a devitalizing influence that will lead to conditions closely comparable to those resulting from entire lack of exercise. Doubtless a hundred persons suffer from lack of exercise, however, where one suffers from over exercise. So the practical lesson that one is commonly called upon to inculcate is that exercise is the road to health.

Vigorous exercise is a recognized factor stimulating formation of blood corpuscles; which fact, according to the present theories, suggests a fairly direct association between exercise and prevention of the disturbances of protein metabolism that are here postulated as constituting the true cancerous condition.

Whereas lack of exercise and improper diet are, in my opinion, the chief causes that lead to the maladjustments of metabolism constituting the cancerous condition, there are, as a matter of course, many minor causes of disturbance. Conspicuous among these is the loss of blood which many women suffer at the menopause; a condition that no doubt contributes very markedly to the genesis of malignant neoplasms; a condition, therefore, which

Digitized by Google

should always receive careful attention from the physician. Any condition that causes persistent anæmia should be viewed with solicitude in this connection.

A greater or less degree of instability conditioned on heredity, is implied as a matter of course, as determining a "tendency" to cancer. Hormone disturbance (e. g., thyroid inefficiency) may also constitute a predisposing element.

As to causes that determine the localized development of a neoplasm, when the cancerous condition eventuates in such development, elaborate studies have been made, and there is virtual unanimity of opinion among authorities. Any chronic source of irritation may result—and indeed must result—in stimulus to growth of new cells. A callous on the thumb and a corn on the toe illustrate this principle as tangibly as an epithelioma on the lip where a clay pipe has long been held, or a carcinoma of the breast that developed from a nipple irritated by a corset steel. But the thumb callous and the corn are "benignant" growths because their tissues are not of a character to be broken down by the bodily enzymes. The same is true of an ordinary overgrowth of fibrous tissue in the interior of the body, as a fibroid of the uterus or a fibroma located, for example, on the forearm.

The new growth, let it be emphasized, becomes malignant only when its character is such that its cells can to some extent be hydrolyzed by the bodily enzymes (including, prominently, according to present thesis, the enzymes of the white and red corpuscles). Moreover, even cells falling within this definition are not necessarily a menace to the system, provided the supply of enzyme-forming corpuscles is adequate and in good working order; for in that case misplaced new cells are at once dissociated and the products of such dissociation utilized as animo-acids or eliminated from the body. According to the proteomorphic theory, the early stages of such dissociation are effected by the white corpuscles, and the later (polypeptid) stages by the red corpuscles; but details as to this are not essential to the present thesis. What is essential is the recognition that if the enzymes that are competent to hydrolyze cells, whenever these cells are present in excess, are normally abundant in the system, there will be no development of a malignant neoplasm.

Stated otherwise, the presence of the tangible "malignant" neoplasm is in itself evidence that there was antecedent disturbance of the processes of protein metabolism in the body, characterized specifically by inadequacy of the enzymes that deal with proteins not needed by the system.

Viewed from a slightly different angle, it appears that any proliferation of new cells, however induced e.g., in repair of an

Digitized by Google

ordinary traumatism—is a potential malignant neoplasm; the question as to whether it becomes an actual menace being determined solely by the antecedent conditions of bodily metabolism. As illustrating the truth of this, it is familiarly known that normal blood antagonizes cancer cells when introduced from without, as in the case of an inoculation experiment in animals. It is known, too, that transplantation experiments are facilitated by bleeding the animal in advance of transplantation.

Summarizing the matter, we may say that three factors are always present and in cooperation when a malignant neoplasm develops in the human subject. There is (1) the factor of disturbed protein metabolism, which I have spoken of as the cancerous conditions; there is (2) the factor of local irritation,—a pipe stem on the lip, an injury to the breast, hot food in the mouth or stomach, chronic intestinal irritation, a laceration of the cervix uteri; and there is (3) the factor of inherent susceptibility, hereditary or acquired.

It is the old story of stress and resistence. The same irritation being applied in the same place in the case of two individuals, one individual suffers no obvious inconvenience, because his defensive mechanism is in good working order; and the other individual develops a fatal "cancer" because his defensive mechanism is not in effective fighting condition.

This view harmonizes the contentions of those theorists who have on one hand alleged the general origin and on the other, the local origin of cancer. In a sense both theorists are right, inasmuch as there would probably never be a local neoplasm developed in any individual case, unless there was some source of irritation. So there is every reason why careful attention should be paid to sources of local irritation, and to local injuries of every character. But it is sheer folly, while treating these local conditions, to ignore the underlying systemic maladjustments, correction of which (where this is possible) would make the danger from local irritation negligible.

In other words, in the profounder view, the problem of the origin, and therefore the problem of the prevention, of cancer implies attention to the bodily processes of metabolism—digestion, assimilation, nutrition. Mere attention to local conditions partakes of the character of what Thoreau called clipping at the twigs of the tree of evil while the roots remain untouched. The root of the cancerous condition is disturbed protein metabolism, and not mere local irritation.

I shall have occasion to point out rather obvious corollaries of this view in their application to the question of the surgical treatment of cancer, as well as to make what I hope may be considered important deductions as to more effective general treatment of the malady.

Digitized by Google

SECTION III

THE LOCAL AND SURGICAL TREATMENT OF MALIGNANT NEOPLASMS

We have seen that the development of a local neoplasm implies defective conditions of general blood supply.

Such deficiencies may be accentuated by local perversion of circulation, as, for example, where the capillaries and veins are rendered patulous by the persistent application of heat, as in the use of a clay pipe, or of the abdominal heaters carried by certain natives of the Orient.

In a slightly different way, the presence of an excess of adipose tissue, may interfere with the circulation, and tend to produce a local anæmia even while the general blood supply is fairly adequate.

In a case in which the general conditions of protein metabolism were just at the border line, so to speak, of the cancerous condition,—that is to say, of out-and-out abnormality,—a comparatively slight interference with circulation at some local point may give opportunity for the development of a neoplasm that otherwise would be held in check.

Such a condition is found, for example, in nearly all scar tissue. Every pathologist knows that scar tissue is poorly supplied with blood vessels, and that it tends rather readily to break down under irritation. In other words, it has not a normal degree of resistance. Doubtless this lack of resistance is closely associated with the defective blood supply. If, now, in addition, there is some source of irritation that tends to stimulate the growth of the cells (as all irritation does tend to do), conditions are favorable for the development of a neoplasm, which will be non-malignant or malignant according to the general condition of the blood, or according to the precise character of the new tissue itself.

If the balance of leucocytes is right, and there is an adequate supply of red corpuscles to deal with the later products of protein decompounding, the new tissue will be cared for by the system, and the condition of malignancy cannot develop.

If, on the other hand, the red cells are inadequate either in number or in activity, the development of the new cells will almost of necessity result in a condition of malignancy.

Even when at the outset the red cells are adequate the growth of the new tissue may be so rapid as to supply a larger amount of protein than can be dealt with (particularly if the red cells

Digitized by Google

are over-burdened by an excess protein diet), and a condition that at first was non-malignant will gradually grade into malignancy.

Such a change from a benign to a malignant condition is a matter of common observation. As an illustration, note how ulcer of the stomach tends to develop into cancer of the stomach. The presence of the ulcer tends in itself to interfere with digestion and assimilation, and thus to superinduce the systemic maladjustment, as regards protein metabolism, which I have all along spoken of as the cancerous condition. In this case, the initial cause of the entire difficulty may have been the ingestion of a morsel of hot food. The local abnormality here precedes the systemic one; but it should be recalled that in such a case, if the person swallowing the hot morsel of food was in normal health, the original stomach lesion was an ulcer of "benign" character, and its ultimate malignancy was sequential to the general condition of protein maladjustment, as in the case of every other malignant neoplasm.

Cancer of the stomach, however, is a case apart, complicated by the fact that the stomach is the channel of intake of foods to nourish the body in general. With malignant neoplasms in general, it is a safe presumption that there are usually deficiencies of local circulation to supplement the defects of the general blood supply. The uterus depleted by hemorrhage is an illustration in point.

It follows that anything which tends to facilitate the circulation of the blood in and about the malignant neoplasm may be of remedial value, provided that the enzymic conditions of the blood have not shrunk to too low a level.

So we find that a local inflammation may sometimes have curative effects at the early stage of development of a malignant neoplasm. The cardinal symptoms of inflammation—pain, redness, and swelling—are associated with an engorgement of the blood vessels, and thus with an increased local capacity to deal with the protein elements. The true explanation of inflammtion has probably never hitherto been available as clearly as the proteomorphic theory reveals it. Hitherto no one has understood just why there should be an accumulation of red blood corpuscles at a source of inflammation. That the process was curative or beneficial for the individuals could be taken for granted, but as to just what the nature of the benefit inferred might be, has hitherto been only inferential. Now that the province of the red corpuscles in dealing with the end-products of protein metabolism is understood, the benefits of the inflammation induced, for example, by bacterial onslaught are clearly explicable. The province of the red blood corpuscle is to cooperate with the white corpuscles by carrying away and further proteolyzing the later products of protein decompounding.

Digitized by Google

Where the protein in question is new tissue of cancerous character, the process of decompounding and elimination is of course entirely comparable. The leucocytes (in particular, probably, the large mononuclears) begin the process of hydrolysis, and the red corpuscles continue it beyond the polypeptid stage and carry away the toxic by-products.

So we might expect a certain amount of relief, and even in favorable cases an actual curative process, to be engendered by local inflammation, however induced, in the region of a malignant neoplasm at an early stage. Such an expectation is occasionally justified. We have recently had under observation at the Beebe-Williams Clinic a case in which an accidental streptococcus infection resulted in the disappearance of an epithelioma of the lip quite without treatment; and this observation is by no means unprecedented. Doubtless there are scores of irritative or caustic compounds that have in exceptional instances produced the "cure" of a local epithelioma, or of a carcinomatous ulcer of the breast, through inducing such a local inflammation.

Such cases, however, would obviously be exceptional, and in general it is to be hoped that a local inflammation will prove curative in any case of a well-developed malignant neoplasm only in occasional instances. As an adjunct to general treatment, however, the application of a local irritant may be of value. But at best this treatment must be considered as an adjunct only.

It is my belief that much the same statement may be made with regard to the efficacy of the treatment of the local neoplasm with the knife. I am aware that this view is heretical, but it follows as a natural conclusion from the line of reasoning above outlined.

To be sure, it is current surgical doctrine that if cancer can be removed early enough, and removed in its entirety, the patient is cured.

But in point of fact, if the present thesis as to the nature of cancer is tenable, the surgeon who has removed a malignant neoplasm,—even in its earlier stages, and even though the removal had been as complete as is ever feasible,—far from curing the malady, has not really treated the malady at all. He has removed a local manifestation of the essential systemic abnormality that is the true "malignant condition," but at best the treatment is a tentative dealing with symptoms, and has no reference to the essential disease itself.

It is true that the removal of the local neoplasm takes away a certain amount of tissue that, through partial dissolution, is poisoning the system; and thus may be a valuable aid in the treatment of the amaladjustment in the process of nutrition, which constitutes the essential character of cancer. But to treat the

Digitized by Google

local condition, and imagine that in so doing one has cured the malady, is hardly less futile than would be the supposition that one has cured a case of syphilis because one has excised a syphilitic wart or healed a chancre or a tertiary ulcer by local cauterization.

The futility of even the most drastic surgical interference is illustrated by the history of a case recently examined at the Beebe-Williams Clinic in which both breasts and the axillary glands had been removed because of the presence of small nodules which were pronounced of doubtful malignancy by a competent microscopist; yet in which the blood six months later recorded 17 per cent. of large mononuclear leucocytes, half of them myelocytes, leucoblasts, and lymphoidocytes; together with red cells showing poikilocytosis and polychromasia, and not infrequent normoblasts, evidencing a condition of myelogenous excitation that—in connection with the history of the case—left one not at all in doubt as to the existence of the cancerous condition. Here surgery had been given the best possible chance, and had obviously failed.

It does not follow that the surgeon's knife should be held in abeyance. On the contrary, there is the most logical reason for using the knife, and removing as much as possible of the local neoplasm that evidences the systemic disturbance. But such a procedure should be but a small part of the process of treatment of the cancerous condition. In every case where a malignant neoplasm is removed by the surgeon's knife, there should be the most careful examination of the blood, with full count of the corpuscles both red and white, and differential count of the latter. There should be the closest scrutiny of the patient's habits of living, with notable reference to the diet, the condition of the bowels and kidneys, and the general processes of assimilation and bodily metabolism. Only by attention to these, and the readjustment of the perturbed process of assimilation, can there by any reasonable grounds for hope that the excised neoplasm will not recur.

It is partly because surgeons usually fail to give such attention, that the neoplasm does return after surgical removal in so preponderant a proportion of cases. That it ever fails to recur must be ascribed to the good luck of the patient, or to his chance observation by an internist of discrimination and judgment, rather than to any merit of the average performer of the operation.

I shall have something more to say presently about the preoperative and post-operative treatment of malignant neoplasms, suggesting, among other things, that any surgeon who fails to avail himself of therapeutic measures now available for general treatment of the case in connection with his operations must be

Digitized by Google

judged guilty of gross negligence, amounting to malpractice. But this presentation of the case may advantageously be delayed until discussion has been had of the new therapeutic measures in question.

SECTION IV

"BIOLOGICAL MEASURES" IN THE TREATMENT OF CANCER

As preliminary to such discussion, it will be well to take a brief survey of various tentatives in the direction of the general treatment of cancer, made in recent years, that have seemed to have scientific foundation and to meet with a certain measure of success in a limited number of cases; to the end that we may inquire whether there is a point of contact between these different kinds of treatment.

The discovery of such a point of contact would obviously give interesting clues to the further investigation of the subject.

The very brief examination necessary in the present connection may advantageously be conducted along the lines of the classification or synopsis given by Bainbridge, who summarizes what he refers to as "biological measures" for the cancer treatment under the following headings: (1) Bacterial toxins, (2) Antitoxic sera, (3) Antitoxins, (4) "Toxins" or "Fluids," (5) Vaccines, (6) Residues, Extracts, and Emulsions, (7) Serous Exudates (Sera), (8) Opotherapeutic measures.

Among the examples of antitoxin, antitoxic sera, and bacterial toxins, the following are named: (1) Blastomycetic antitoxic serum of Sanfelice, based upon the theory that cancer is due to blastomycetes; (2) Wlaeff's Serum, made from cultures of blastomycetes from cancerous inoculated into pigeons; (3) Serum of Emmerich and Scholl, made by inoculating sheep with *Streptococcus erysipelatosus;* (4) Doyen's Serum, from *Micrococcus neoformans;* (5) Schmidt's Serum, from *Mucor mucedo* (Cancroidin, Antimeristem); (6) Wyeth's Toxins of *Streptococcus;* (7) Coley's Fluid—Mixed toxins of *Streptococcus erysipelatosus* and *Bacillus prodigiosus.*

Among the vaccines named are the *Micrococcus Neoformans* Vaccine (Doyen), used in connection with the serum made from the same organism, and the Bacterial Vaccine of Jacob and Geets, made from cultures of the same micrococcus sterilized and standardized according to the opsonic theory.

Digitized by Google

Residues, Extracts, and Emulsions, include Coca-Gilman Extract, or Emulsion; Vaughan Residue; the Fichera Emulsion, and Autolyzed Cancer or Normal Tissue.

Of serous exudates and body fluids there is a long list, including Hodenpyl's Ascitic Fluid from a cancer subject; Normal human Blood Serum; blood serum of the horse and donkey; Hydrocele Fluid; Spermatocele Fluid; Ascitic Fluid from the subject of alcoholic cirrhosis; Ascitic Fluid from the subject of cardiac insufficiency; and Pleuritic transudate resulting from broken compensation.

Of Opotherapeutic Measures (organotherapy) the examples include (1) "Antituman" of Oestriech made from embryological cartilage and arteries from which a supposedly immunizing substance chondroitin-sulphate is extracted; (2) Thymus Gland Extract; (3) Extract of Sheeps' Thyroids; and (4) Pancreatic enzymes, Trypsin and Amylopsin as widely exploited a few years ago under the auspices of Beard.

As to the status of these various treatments, perhaps I cannot do better than to quote Bainbridge's summary to the effect that: "Many of the agents have been discarded, with practically a consensus of opinion against their efficacy; others continue to receive a certain amount of attention, largely because no definite test of their value has been made upon a convincing basis; while still others are being given careful consideration by a sufficient number of skilled clinicians to warrant the hope that a decision, pro or con, will be soon forthcoming."

I would add, however, that there is a considerable body of evidence to show that a good many of these diverse agents have seemed to produce beneficial effects in a certain number of cases, and that several of them are still actively employed and enthusiastically championed by a number of physicians. Note, for example, the report of Klinger in the *Correspondenz-Blatt für Schweizer Aerzte* for Sept. 23, 1916, on the results obtained with autolysates, to which fuller reference will be made in another connection. That no one of them fully meets the hopes and expectations of its originators may, doubtless, be accepted as fairly demonstrated. But I think it must also be clear that even tentative results would hardly have been attained with so great a variety of animal extracts unless some general principle was involved that gave the different treatments affinity.

It is my belief that the principle in question is the presence of animal or bacterial proteins in all of the various compounds in question. In the case of Beard's Pancreatic Enzymes there are also present digestive ferments closely comparable to those known to be evolved by the white blood corpuscles, the manner of action of which will be dealt with presently.

Digitized by Google

For the moment, the point that I would emphasize is that the entire group of biological cancer remedies as above outlined comprises agents of very diversified origins that have at least one prominent point of contact in the presence of organic proteins.

If we add that among all the numberless agents that have been used in the general treatment of cancer, there is not one at present commanding the slightest scientific consideration that does not contain protein, we are at least put in the way of an interesting and suggestive line of thought.

The ideas thus engendered are naturally linked with the reflection that many students of cancer have attempted to associate the genesis of the disease with defects of protein assimilation; and also with the very interesting studies of Buckley in the treatment of cancer by careful regulation of the diet with reference to the protein intake.

The full bearing of the observation, however, is appreciable only when we reflect along the line of the now familiar physiological principle that the introduction of a foreign protein parenterally leads to a development by the body of antibodies to antagonize the toxic influence of that protein; and the further reflection that the antibodies in question are produced by the system in excess of the quantity required merely to neutralize the foreign agent.

A classical illustration of this is found in the use of the antityphoid vaccine, which leads to the production of antibodies in such excess as to give the individual immunity to the typhoid virus for a term of months or years.

A moment's further reflection shows that the antibodies thus produced when a foreign protein is introduced in the body must be of a character to effect the decompounding of the protein molecule. If the thesis of the Proteomorphic theory is accepted, it follows that the introduction of a foreign protein will result in the increased activities of the white and red blood corpuscles and of the organs that produce these corpuscles. Specifically, we may expect that after introduction of a foreign protein there will be observable a modification of the blood count in the direction of an increase of large mononuclear lymphocytes and red blood corpuscles. We may assume that there is a responsive increase in the quantitative enzymic activities of these corpuscles, and that the aggregate effect exceeds the immediate needs of the system as induced by the invading protein.

In other words, there will remain a residual quantity of enzymes in the blood capable of decompounding proteins.

These residual enzymes obviously constitute an agent capable of attacking other foreign proteins, unless we assume that they

Digitized by Google

are of so specific a character that they can affect only the particular protein that has invoked them.

Have they such specificity?

This, obviously, is an important question. But I think there can be no doubt about the answer. The enzymes that begin the decompounding of the protein molecule are of a tryptic character, closely comparable apparently whether secreted by the digestive glands or by the white corpuscles, and their action is very general. The same enzyme can affect the decompounding of animal and vegetable proteins of the most varied character, as the normal digestion of an ordinary meal in the intestinal tract sufficiently demonstrates. Moreover, it is specifically observed that the white blood corpuscles can attack and destroy bacterial proteins of many types. There are abundant reasons to believe, then, that the enzymes developed as antibodies to any one of the wide range of foreign proteins introduced parenterally may be able to effect the decompounding of other proteins than the particular one introduced.

If, now, we reflect that the cells of a malignant neoplasm are made up of protein which, notwithstanding its close general similarity to that of normal tissues, is in a sense a foreign protein; and, moreover, that these cells because of their newness and rapid growth lack something of the stability of matured normal cells, it is readily explicable that they may be attacked by the protein antibodies in the blood and decompounded.

As suggesting a chemical basis for the expectation that an agent might be developed that would differentiate between normal cells and cancer cells, we may note the researches of Beebe showing that cancer cells have a mineral content in excess of the normal; and, specifically, that the more malignant types of cancer cells are relatively rich in potassium, less malignant ones showing a relative preponderance of calcium; also the fact, to be dealt with in another connection, that cancer tissue is reported as showing only 70 per cent. of the nitrogen content of normal tissue.

If the protein antibodies in the blood come in sufficient quantities, it is even conceivable that the cells of the neoplasm may be altogether dissociated, and the neoplasm itself thus eliminated. But of course so radical a result as this could be expected only in very exceptional cases in which the balance between the normal activities of the corpuscles and the activities of the cells of the neoplasm had not been too profoundly disturbed.

This is perhaps equivalent to saying that success might be expected somewhat in proportion to the stage of advancement of the cancerous condition in general and of the neoplasm in particular.

A highly important complication is found, however, in the fact

Digitized by Google

that the animal and bacterial foreign proteins now under discussion as furnishing the agents to stimulate the corpuscular enzymes, are in themselves more or less toxic bodies. All foreign serums have elements of toxicity, and this may be so pronounced that the aggregate effect of introduction of the foreign proteins may be the opposite of remedial. As a case in point, the introduction of a foreign blood serum may cause active haemolysis, so that the blood count goes down instead of up. But this, properly interpreted, is in itself an evidence of such activities of a foreign protein as are above postulated, the destruction of the red blood corpuscles evidencing exactly such activities in connection with the elimination of the byproducts of hydrolosis of foreign proteins as is postulated in the Proteomorphic Theory.

But it is obvious that from a therapeutic standpoint the relative toxicity of the protein introduced is of paramount importance. And this observation furnishes the clue to a comprehensive criticism of the entire list of biological agents, above referred to as comprising the various cancer remedies. The bacterial agents employed in making the various serums of Emmerich and Wyeth and Coley are confessedly toxic; and the various and sundry animal serums are all known to have active toxicity when introduced into heterologous parenteral systems.

Hence in practice it happens that in using any of these various vaccines and serums we are introducing agents capable, to some extent, of combating the cancer cell (indirectly), but also agents that put a severe tax on the enzyme-forming organs (blood corpuscles and cytogenic apparatus) they are designed to aid. In using these agents, then, there is always danger that when we take one step up the hill we shall slip back the length of two steps. In other words, while we are by way of "curing" the cancer, we may kill the patient.

As I have already suggested, it is only in a small residual minimum of cases that we can hope to find the balance of nutritional conditions in the system such that, when by a happy chance we stumble on the right dosage of foreign protein, the aggregate results of our effort is beneficial, and the local neoplasm is caused to regress.

Nevertheless, the evidence of these scattered and isolated cases, in the midst of the great mass of failures, is in the highest degree encouraging and enheartening, because, properly interpreted, it tends to establish the general principle that the use of foreign proteins may be of value in the treatment of the cancerous condition. Even though the entire list of "biological remedies" should stand condemned, these tentative remedies will have served a useful purpose in pointing the way to a line of medication which retains their advantages and eliminates their disadvantages.

Digitized by Google

SECTION V

VEGETABLE PROTEINS IN CANCER TREATMENT

It is my opinion that we are already far advanced on the road thus pointed out, and in support of that opinion I purpose now to introduce a body of new evidence.

This evidence concerns the use of proteins in the treatment of cancer, and hence has to do with remedies that are to that extent linked with those that have just been discussed; but from another point of view it may be considered that the treatment about to be discussed is a radical departure, inasmuch as the proteins that it employs are neither toxic bacterial proteins nor animal serums, but relatively nontoxic proteins of vegetable origin. I use the qualifying word "relatively" in a broad, biological sense—to cover the view that all foreign proteins are in a sense toxic. But I should explain at once that the vegetable proteins in question are toxic only in this comprehensive sense; in the ordinary acceptance of the term, they are absolutely nontoxic. That is to say, they could be taken into the stomach in any quantity without producing obvious effect; their toxicity when introduced into the parenteral system is merely of that general type known as anaphylactic.

At this point I would again refer the reader to my paper of October 2, 1915, in the *New York Medical Journal,* where the question of the effect of nontoxic vegetable proteins introduced hypodermically in the treatment of malignant neoplasms was comprehensively discussed for the first time, so far as I am aware. Subsequent experience adds to my belief that the foundations there laid were sound and valid. But the present discussion assumes a more general character than was then possible; because at that time I was basing my deductions on observations made with a single extract (containing, however, a combination of vegetable proteins), whereas at present I am able to tell of experience with vegetable proteins of widely different origin.

The reader of the paper of October 2nd, will recall that, whereas the chief discussion had reference to vegetable proteins, it was also suggested that some of the observed effects of the treatment might be due to the presence of other constituents of the extract, notably chlorophyll. I now wish to add that, whereas we are not yet in position to say positively that there are no agents other than the proteins in the compound that have therapeutic action, yet the trend of our investigation leads us more and more fully to the conclusion that the active agent is the protein, and that the

Digitized by Google

other agents are therapeutically neglible. The evidence for this view, so far as for the present available, will be presented in another place.

Before telling of the laboratory experiments through which we have endeavored, in recent months, at the Beebe-Williams Clinic, to determine the exact character of the remedial agencies in the vegetable extracts in question, let me briefly rehearse the history of the introduction of the new agent, and summarize the results of its use in the hands of more than 1,000 regularly qualified practitioners of medicine.

As preparatory to this, let me say that I have at no time regarded the original proteal compound as a final agent in the treatment of cancer, but only as an important beginning. I have at no time supposed that the particular combination used of the twelve vegetable agents (already named) had unique significance. My personal observation had shown me that the extract produced extraordinary results in a certain number of cases of inoperable cancer, in the hands of other practitioners, at a time when I had no knowledge whatever of the nature of the extract. When the components of the powder from which the proteins were extracted were made known to me, I at once expressed the opinion that we had to do with a general principle and not with anything in the nature of a cancer specific. I ventured the prediction that it would soon be possible to make an equivalent extract from any one of a hundred vegetable substances exclusive of anything in the present compound, and I may now state that this prophecy seems on the way to fulfilment.

In the course of the present paper I shall tell the exact details of production of proteals which, in the opinion of Dr. Beebe and myself, are the close equivalents of the original extract yet which are made from totally different substances,—for example, from alfalfa seed, alfalfa meal, hemp seed, and rape seed.

The essential constituents of these new extracts, as the reader of the above discussion will readily divine, is the vegetable protein content.

The method of extracting these proteins is simplicity itself. It may be repeated in any chemical laboratory, and our clinical results may be tested in any cancer hospital or by any qualified practitioner who has a cancer patient.

But as to this also I shall have more to say after I have told sequentially the story of the evolution of the discovery, and in particular have summarized the evidence as to the remedial value of the original proteal compound, through observation of which I was led, personally, to take up the practical investigation of the cancer problem.

Digitized by Google

The Story of the Original Proteal Mixture

The story of the introduction of the original proteal extract is a very singular one. As I have written a comprehensive history of science, I may claim a fair measure of familiarity with the records of the growth of ideas; and I do not hesitate to affirm that there are few stories more singular than this one in the history of progress. Yet, on the other hand, it may be said to be in a sense typical, inasmuch as an ultimate discovery of altogether unpredicted character grew out of empirical observations that in themselves had only the remotest bearing on the fundamental principle involved.

The discovery to which I refer is the principle that nontoxic vegetable proteins, introduced into the parenteral system, have remarkable remedial value in the treatment of the cancerous condition.

The empirical observations that furnished the point of departure for the investigations that led to the discovery were made in connection with the strangely assorted compound of twelve vegetable substances just referred to ground into a powder and applied as a poultice in the treatment of superficial cancers.

The formula for the vegetable compound in question was devised and brought to this country by a young Hungarian, Alexander S. Horovitz, Ph.D. The compound, when applied as a poultice, seemed to produce beneficial effects in connection with superficial epitheliomas and carcinomas.

Such was the opinion of Dr. Silas P. Beebe, after an open-minded investigation of the subject. So strongly impressed was he with this view, that he suggested to Dr. Horovitz the making of an extract from the powder suitable for hypodermic injection, that he might observe what would be the effect when the essential constituents of the compound were thus introduced directly into the cancerous tissues.

No one in America has greater competency for such an investigation than Dr. Beebe. He holds the earned degrees of B.Sc., Harvard, and A.M. and Ph.D., Yale, vouching for years of special investigation in physiological chemistry and antecedent to special medical training which added M.D., Cornell to the list of his academic titles, and prepared him for the discoveries in thyroid therapy and cancer experimentation that led to his appointment as Professor of Experimental Therapeutics at Cornell University Medical School.

In February, 1915, an extract suitable for hypodermic use was in hand, making it possible to test the merits of the compound in a new way.

The tests were made at the General Memorial Hospital, at the

Digitized by Google

Polyclinic Hospital, and in Dr. Beebe's private office; and a preliminary account of results attained was given in an article published in the *New York Medical Journal* of May 15, 1915.. This must be regarded as a paper of historical importance. It is reproduced in full elsewhere in the volume of which this monograph forms a part.

I shall not now enter upon the story of the controversial aspects of the discussion aroused by Dr. Beebe's paper,—albeit that story is an interesting one, and one that I purpose to tell in detail in connection with the forthcoming third edition of my *History of Science*. Suffice it here that there was no lack of interest on the part of the profession at large, and that the skepticism of persons in authority who pronounced judgment without testing the remedy—in characteristic fashion—retarded progress as has always been the case with every new movement in any field of science.

Nevertheless it was possible six months later to tell of the progress of the new treatment in a series of papers published in the *New York Medical Journal* of October 2, October 9, and November 13, 1915, in which it was made evident that the results attained by the originators of the treatment were susceptible of ready verification at the hands of numerous independent observers. In the concluding paper of the series, published November 13th, I summarized the preliminary results attained in the treatment of 766 cases of inoperable cancer by 152 physicians.

These were all cases of far-advanced malignancy, mostly post-operative. Many of them had been X-rayed and radiumed. All were pronounced inoperable before the proteal treatment was undertaken; and this treatment was used to the exclusion of any other. The preliminary results, as tabulated in the article in question, showed that 16.5 per cent. of the cases in question were reported as having died; 19.5 per cent. as being unimproved; and 64 per cent. as being improved to a greater or less extent.

Following the summary, this comment was made:

"As most of the patients in question have been under treatment for periods of only from two weeks to two months; and as by far the greater majority of them were in very desperate state at the time when the treatment was undertaken, it must be admitted that this is a very gratifying showing. It is perhaps unnecessary to add that, despite the favorable showing, most of these cases are not as yet at a stage where prediction can be made as to the ultimate outcome.

"The conclusion seems unavoidable that Autolysin tends to stimulate or produce a systemic condition unfavorable to malignant neoplasms of every type, and hence favorable to the patient, and that in cases that have not progressed too far before the treatment is undertaken, the attack made upon the neoplasm in

LANE LIBRARY Digitized by Google

response to the action of the remedy is so vigorous as to result in its complete regression and the elimination of its hydrolyzed product from the body; together with the coincident restoration of the patient to a condition of seeming health."

When this article was reprinted, in response to the many requests, a note was added in which certain details were given as to the effect of the remedy on specific symptoms, as observed by the 138 physicians reporting who had used the remedy quite independently of Dr. Beebe's supervision. The facts here summarized were not included in the original article simply because the reports had come to hand so late that their findings could not be introduced in detail on the proof of the article without disturbing the makeup of the journal. I reproduce here the summary as incorporated in a footnote in the reprint of the article:

"The 272 cases treated by 138 different physicians above tabulated were officially reported by the various physicians in response to a request from Dr. Beebe for records to place before the New York Board of Health when that body contemplated making an examination of the treatment in accordance with Dr. Beebe's wishes.

"The reader is aware that among the conspicuous effects of the remedy, as noted by Dr. Beebe and his associates from the outset, are the following: (1) Marked alleviation of pain; (2) The modification or annulment of malodor; (3) Modification in appearance, character, or size of the neoplasm itself; (4) Marked improvement of general health, as to appetite, sleeping, color, weight, or strength; (5) Favorable modification of the mental attitude of the patient. It was desired to ascertain the extent to which alleviation of these symptoms was noted by the independent physicians who were using the treatment. So specific inquiries as to these points were included in the questionaire sent out by Dr. Beebe.

"The specific answers to these questions constitute one of the most interesting features of the reports. They may be summarized thus: Where pain was present, it was favorably modified by the treatment in 78.2 per cent. of cases; where malodor was present, it was favorably modified in 85.7 per cent.; the size or condition of the neoplasm itself underwent favorable modification in 69 per cent. (with conspicuous regression in size in 30 per cent.); the general health of the patient was benefited in 71 per cent.; and the mental attitude in 73 per cent.

"Dealing, as the statistics do, with supposedly hopeless cases, in the presence of which the physician has hitherto stood powerless, and with symptoms mostly not susceptible of amelioration by any agency hitherto available, this is a showing that is amazing and enheartening."

The reports above summarized bore date of approximately November 1, 1915. In the year that has elapsed since then the progress of the proteal treatment has been from one point of

Digitized by Google

view gratifying; from another humiliating. It is gratifying, because about 800 additional physicians—all of course men of recognized professional standing—have tested the remedy in their private or hospital practise in the treatment of about 2,000 cases of inoperable cancer with singular unanimity of results; humiliating, because in the same interval, 75,000 or perhaps 80,000 individuals have died of cancer in the United States who, through ignorance or conservatism on the part of their medical advisors, have been denied the benefactions of this treatment.

The latter aspect of the matter, however, is after all only a typical instance in the familiar story of human prejudice and conservatism, and need not concern us here. What does concern us is the record of results attained in the treatment of the 2,000 cases who chanced to come into the hands of physicians of the more open-minded or more alert-minded minority.

That is a question of very obvious interest and importance. I shall attempt to answer it in the frankest and most unprejudiced manner. I have studied the reports of these cases, not to make a brief for the new treatment, but to see what they could teach me. Elsewhere the evidence is presented in detail; here I may summarize it by saying that it gives the fullest and most unequivocal substantiation to the conclusions based on the study of the earlier cases, as above detailed.

It should be explained that no comprehensive and uniform report at a fixed date has been made by the 800 physicians whose work is now under consideration. Their reports have come from time to time, and in the form usually of personal letters,—letters not designed in any case for publication, and for the most part written in the interest of the individual patient, asking advice as to some detail of treatment very commonly, and containing expressions of opinion as to the progress of the case of precisely the character a practitioner would make in seeking the advice of a special consultant.

It must be evident, I think, that reports made under such circumstances have peculiar value. In the nature of the case, they are candid, frank, and uncolored. They state the facts as the observer sees them. The observer is a regularly qualified practitioner in good standing in the profession. That in general the men who make these reports are above the average of the profession is implied in the fact that they are men who trust their own judgment to the extent of being willing to test new remedies, and do so often in the face of opposition or even ridicule on the part of professional brethren. More than four hundred of them are members of the American Medical Association.

On the other hand, it must be borne in mind that, by the same token, these men are for the most part not specialists of wide

Digitized by Google

experience in the treatment of cancer cases. A number of them are such, to be sure, but in the main the physicians of the group under consideration are general practitioners. But in a way that makes their testimony all the more important, inasmuch as it shows what the new line of treatment may be expected to accomplish in the hands of the average practitioner. One of the greatest merits of the proteal treatment is that it enables isolated physicians, in the remotest hamlets, to do something tangible and definite toward ameliorating the condition of the cancer patient who has passed beyond the reach of the surgeon.

Thanks to the new treatment, the most inexperienced practitioner can do more to-day for the amelioration of the condition of a late stage, inoperable cancer case that could hitherto be accomplished by the most experienced practitioner in the best metropolitan cancer hospital.

The substantial unanimity of opinion as to the character of results attained in their own practice by some hundreds of physicians scattered about the country, and in foreign countries, is so striking a phenomenon that it is susceptible of but one interpretation. It is impossible that all these men should be mistaken. Their individual observations, when aggregated, pile mountain high the evidence that the proteal treatment has remarkable effect in relieving pain of the inoperable cancer subject; removing the bad odor of cancerous discharges; improving the general health of the patient; and conspicuously modifying the condition of the malignant neoplasm.

After carefully scrutinizing the evidence, it is difficult to avoid the conclusion that these beneficial effects of the proteal treatment, in varying degree, may be observed in an overwhelming proportion (not less, in my opinion, than 80 per cent.) of cases of inoperable cancer, wherever located, in which the remedy is administered in suitable doses.

This, it will be observed, postulates nothing as to the ultimate effects of the treatment. It says nothing as to the "cure" of cancer. As to that, I shall have something to say in detail a little later in the present monograph. Here it suffices to note that the records under consideration tell of definite and unequivocal improvement of the most tangible character in a large proportion of cases; such improvement amounting in a certain number of cases to seeming clinical recovery.

Perhaps we may gain as clear an idea of what may be expected of proteals in the treatment of the class of hopeless and inoperable cancer hitherto available, in the most skilful hands, by citing the results recorded to Dr. E. H. Williams, of Los Angeles, California, in sixty-five consecutive cases treated by him in private and hospital practice as reported June 7, 1916. The results

Digitized by Google

are: 14, or 21 per cent. not improved by the treatment; 20, or 30 per cent. temporarily improved; 17, or 26 per cent. conspicuously improved; and 14, or 21 per cent. apparently clinically recovered or on the way to recovery. All the cases in question were cases of inoperable and seemingly hopeless cancer, diagnosed by other physicians and brought by them to Dr. Williams for treatment.

It may perhaps be questioned whether a corresponding showing was ever made with a similar number of cases of inoperable cancer correspondingly advanced, by any other method of treatment whatsoever.

SECTION VI

LIMITATIONS AND EXTENSIONS OF PROTEAL TREATMENT

Such a record cannot be considered as other than encouraging and stimulative in the highest degree. But of course this is far from saying that it constitutes an ideal record. It represents a good beginning, but it leaves us still far from the goal of which optimists have dreamed,—the conquest of cancer.

Of course it must not for a moment be overlooked that the cases hitherto treated—or at all events the great majority of all the three thousand or more to whom the original proteal treatment has been administered—were so far advanced that there was no reasonable hope that the treatment could be more than palliative. No physician needs to be told that there are conditions of disrepair that places the human machine beyond the possibility of restoration. A large proportion of the cases had reached this stage. The most that could be hoped was that the individuals would be made more comfortable and their lives somewhat prolonged. This hope has been abundantly justified in a great majority of all the cases treated.

Naturally the patients themselves, and their friends, were hoping not merely for relief, but for a "cure" of their maladies. But no one speaking with authority has ever referred to the Horovitz-Beebe proteal as a cure for cancer. As I have elsewhere remarked, it is a scientific remedy, not a magician's wand. It must not be expected to accomplish the impossible, though in some cases the results of its administration have seemed almost magical. The really important question at issue is not whether the proteals can be expected to "cure" the types of incurable cancer to which they have hitherto chiefly been applied; but what they can accomplish in more favorable cases.

In considering that question, we are brought face to face with certain limitations seemingly inherent in the proteal method,—

Digitized by Google

assuming, for the moment, that my interpretation of the action of the remedy as chiefly dependent upon its protein content is the correct one. The essence of this important complication is that when foreign proteins are introduced into the system in successive doses hypodermically, the system develops an increasing degree of tolerance or immunization, so that it is necessary to increase the dosage, if maximum results are to be attained. Meantime there were complications in connection with the administration of the original extract that until recently have made it difficult in many cases to administer the remedy as frequently or as freely as could be desired.

Chief among these complications was the fact that the original extract (known as Autolysin Horovitz-Beebe), caused a very severe smarting or burning pain at the point of injection, which some patients found almost unbearable. Moreover, in many cases there remained at the point of injection, sometimes for days and even weeks, a certain amount of unabsorbed matter, as a source of irritation producing tender and even painful lumps or nodules. These, to be sure, almost invariably disappeared without leading to the production of abscesses, but they constituted an annoyance to the patient that militated against the treatment.

It is probable that this was partly due, in the original preparation, to the presence of a considerable quantity of chlorophyll. The chlorophyll was largely eliminated from a subsequent preparation, and the administering of this was found to be in the main much less painful, although still markedly disagreeable.

Very recently it has been found that by preparing the remedy by modified methods, in which the use of alcohol is altogether omitted, and in which the acidity of the final product is completely neutralized with sodium hydroxide, a further improvement has been effected, and the remedy as we now employ it (known as Autolysin Horovitz-Beebe-Williams) produces no pain whatever, on injection—beyond the negligible sensation produced by any use of the needle—and a relatively mild local reaction with no unpleasant local sequelae.

The new method of extraction from which this improved extract is produced has elsewhere been described in detail. Briefly, it consists essentially of the use of sodium hydroxide solution as a solvent; or, as an alternative, of a salt solution with the subsequent addition of sufficient sodium hydroxide to neutralize the solution. I may add that other methods of modified protein extraction are under investigation, but not yet at a stage of development at which it can be confidently affirmed that their product is in all respects equal to the extract produced by the older method.

Digitized by Google

A NEW SERIES OF VEGETABLE PROTEIN ANTIGENS

Even where the local reaction is of such a character as to permit the administration of frequent and larger doses of the proteal compound, it is not infrequently observed that the conspicuous and rapid improvement that marks the earliest administration of the remedy ceases presently to be cumulative; a condition of stasis being reached which is discouraging to physician and patient alike.

The patient's condition of general health and comfort may be at a much higher level than before treatment began; and there may have been marked improvement in the character of the local neoplasm; yet it may appear that the remedy has lost its power to assist the patient farther,—just at a time when there seemed hope that a very slight additional impulse might put him on the road to ultimate recovery.

It is a not unnatural assumption that in such a case the patient has come to a stage at which the enzymic response to the particular vegetable proteins contained in the extract has reached its maximum; and that in this particular case the development of new cancer cells now equals or exceeds the rate of decompounding of cancer cells effected by the enzymes in question. And it is equally natural to inquire whether it might not be possible by the use of proteins of a different character from those previously administered to stimulate a new phase of enzymic activity and thus supplement the work, and perhaps turn the scale in favor of the battling corpuscles and against the cancer cells.

Acting on this assumption, Dr. Beebe and I have prepared a series of extracts of vegetable proteins from plants not used in making the original extract. The first of these, and the ones that hitherto have been given the fullest trial, are prepared from the seeds of the Alfalfa plant (*Medicago sativa*), Indian hemp (*Cannabis Indica*), and Rape (*Brassica Napus*).

One method of extraction consists of treating the ground alfalfa seeds with a solution of sodium chloride, neutralizing, filtering through paper and a Birkefeld filter, and standardizing on the basis of three milligrams of nitrogen to the cubic centimeter. By another method, the extracted protein is precipitated with hydrochloric acid, washed, and the approximately pure protein redissolved in sodium hydroxide. It is obvious that the former method may incorporate certain substances—conceivably vitamines among others—in the ultimate product that are eliminated by the second process. Elaborate tests are being made at the Beebe-Williams Laboratory and Clinic to determine whether the solution of pure protein acts as effectively as the solution containing the other components.

Digitized by Google

It is convenient to have some general term descriptive of proteins of any character used singly or in combination, as antigens to stimulate the bodily defenses. I have suggested the word "Proteantigens" as such a generic term. For vegetable proteins as a class, I suggest the name "Proteals." It chanced in our laboratory work the solution of pure protein of alfalfa bore the designation, "Proteal No. 6"; hemp protein was "Proteal No. 13"; rape protein, "Proteal No. 24"; and a mixture of proteins from alfalfa meal was "Proteal No. 28." A combination of proteals Nos. 6, 24, and 28, was designated "Proteal No. 30."

In recent months, we have administered these new proteals to patients who had been for a considerable period of time under the original proteal treatment, and who had been in a measure immunized, as well as to patients not previously treated with proteins of any kind. The hypodermic injection of the Beebe-Williams proteals produces no pain, and a mild local reaction. The alfalfa protein in particular is likely to produce a marked general reaction, of typical anaphylactic character, within a few hours after administration, though patients differ considerably as regards their susceptibility.

Patients who had ceased to have any reaction when taking daily doses of 25 to 30 or even 40 minims of the Horovitz-Beebe proteal have shown pronounced reaction on receiving the first dose of 8 or 10 minims of the alfalfa extract of standard strength.

A cancer of the breast in which the pain was not entirely controlled by the original proteal experienced marked relief within a few hours after the first dose of "Proteal No. 6." In another case, there was conspicuous reduction in the size of a metastatic supra-clavicular nodule after the first dose of the new proteal, this nodule having been stationary in recent weeks under the administration of the original proteal compound.

We are not yet ready to report in detail as to the use of these new proteals. But enough has been done to justify the hope that the theory of the possible lifting of the cancer patients stage by stage by the sequential use of different vegetable proteins may not be without foundation. Observation suggests that, in many cases, the maximum response to a given protein is reached in about six or eight weeks; and we are working along the lines of the assumption that it may then be desirable to substitute a new protein (or mixture of proteins) during another term of six or eight weeks; ultimately using a third or fourth proteal if necessary.

It is highly interesting in this connection to note the experience of Klinger in the treatment of cancer with animal autolysates, to the effect that a given autolysate seems sometimes to lose its power, but that "this can be obviated by changing the material,"

Digitized by Google

—that is to say, by using proteins extracted from a different organ or tissue.

Conceivably it may be better to alternate day by day, or to give several proteins at a dose. A prolonged period of clinical experience will be necessary to determine such important details as these.

Meantime it is not suggested that the therapeutic possibilities of any individual proteal are exhausted after a brief period of administration. A study of the blood charts to be discussed in detail presently suggests a period of what might be termed "negative phase" following the early maximum response: but this in turn is followed by a period of renewed activity that may con-

TABLE III.—ORIGINAL CASES AT THE BEEBE-WILLIAMS CLINIC

A GROUP OF CASES OF INOPERABLE CANCER STILL UNDER OBSERVATION AND IN ROBUST CONDITION AFTER PROLONGED PERIODS OF PROTEAL TREATMENT (311 TO 527 DAYS; AVERAGE, 416 DAYS)

Case No.	Name	Nature of Case	No. of Days	Hemoglobin	Red Blood Corpuscles	White Blood Corpuscles	Polynuclears	Mononuclears		Eosinophiles	Basophiles
								Large	Small		
278	Mrs. B...	Rec. C. of Breast.....	105	90	4,400,000		58.6	19	20.6	1.6	0
			180	100	5,408,000	7,500	72	17.3	8.6	2	0
			194	100	4,832,000	6,100	54.5	34	11.5	0	0
			475				57.4	13.7	26.3	1.7	0.7
16	Miss D..	Rec. C. of Breast.....	93	90	4,464,000		59	17	24	0	0
			198	95	5,664,000	7,600	66.5	21.5	20	2	0
			215	100	5,252,000	7,500	61.5	13	24	1.5	0
			527		3,705,000	6,240	60	13.3	26.6	0.6	0
381	Mrs. H..	Melanoma.....	2	100	4,752,000	7,600	80.5	7.6	8.6	3.3	0
			16	100	4,448,000	8,000	78	10.5	7	4.5	0
			30	100	4,500,000	8,200	81	12.5	5	1	.5
			48	100	5,184,000	8,000	77.5	9.5	11	2	0
			324				67.5	21.5	8.5	.5	1.5
239	Mrs. M..	Car. of Breast.....	142	90	5,376,000	7,200	64.3	16.3	15.6	3.6	0
			155	95	4,800,000	8,800	62.3	21.5	13	2	1
			172	100	5,096,000	8,000	60	23.5	13	2.5	1
			405				58	16	22	4	0
370	Mrs. R...	Ep. Car. of Hand.....	5	95	4,896,000	10,200	72.6	14	10.6	2.6	0
			20	90	4,556,000	10,400	74	10	12	3.5	.5
			45	90	4,130,000	12,000	77.5	15	6.5	1	0
			311				58.4	30.3	5.3	5.4	.1
242	Mrs. S...	Ep. of Face.....	69	75	2,800,000		60	10.5	29	.5	0
			144	95	4,672,000	6,600	55.5	28	14.5	1	1
			155	100	4,672,000	7,200	50.5	31	15.5	3	0
			460				51	9	38.5	1.5	
332	Mrs. V. W.	Rec. C. of Breast.....	50	85	5,008,000	8,880	64	16	24	0	0
			62	100	4,522,000	7,600	58.6	18.6	19.3	2.3	1
			76	100	4,448,000	7,400	55	17.5	15	2.5	0
			90	100	5,656,000	8,900	48.5	27	20.5	4	0
			394				39.3	17.6	41.6	1.3	0
168	Miss W.	Rec. C. of Breast.....	88	80	4,488,000		66.3	11.6	20	2	0
			112	95	4,240,000	8,000	67.3	21.6	10	.6	.3
			121	100	4,650,000	9,200	64.5	13	17	.5	0
			486				52.6	20.3	26	1.3	0
251	Mrs. W..	Rec. C. of Breast.....	63	85	3,570,000		74	11	11	4	0
			138	85	5,280,000	9,400	68	16	9.5	6.5	0
			155	95	4,288,000	8,600	64.5	19.5	12	3	1
			467				63.6	9	20	6.6	
368	Mrs. C...	Rec. C. of Breast.....	1	90	3,976,000	9,280	65.6	14.3	17.3	2.3	.3
			29	95	4,112,000	8,500	64.6	19	12.3	3.6	.3
			44	100	4,576,000	8,900	72	14.5	13	.5	0
			60	100	4,096,000	8,000	61.5	19.5	18	1	0
			312				55.3	16.6	28.3	2	0

Digitized by Google

tinue for a term of months. The point here in question is, whether by changing the protein the reactionary phase may be obviated. The matter will be given fuller consideration when the blood charts are under discussion.

It is essential, of course, to bear in mind the familiar phenomena of anaphylaxis, and to continue the administration of any given protein daily, or at intervals of two or three days at the most, until immunization is attained. It would obviously be inadvisable, after administering a given protein to wait ten days or two weeks before administering a second dose of the same protein; since it is precisely under such conditions that the phenomena of anaphylaxis in its alarming forms are likely to be developed. One protein, as is well known, does not fully immunize the system against another. Indeed, it is precisely this fact, as already pointed out, that furnished the basis for the theoretical administration of a series of proteins along the lines just suggested.

It has been pointed out that there is a wide range of variation among patients as regards their response to a given quantity of any foreign protein. The degree of the susceptibility of individual patients must be determined by experiment. A safe initial dose of an extract containing two per cent. of non-toxic vegetable proteins is 8 or 10 minims, given of course hypodermically.

Ordinarily this dose may be increased from day to day, and it is not unusual to find a dosage of 25, 30, or even 40 minims required to get maximum results. Occasionally, it is necessary to carry the dosage to 60 or even 90 minims. A patient who at first reacted vigorously to a dose of 10 minims, may subsequently be able to take four or five times the quantity without conspicuous reaction.

It should be recalled, however, that in giving these large doses one is introducing a relatively large quantity of foreign proteins and that these proteins must be dealt with by the bodily enzymes. So it may be accepted as a general principle of medication that the smallest dose that will produce a vigorous enzymic (corpuscular) response is the best dose.

There may come a time in the course of any individual case, at which the enzymic response has reached the maximum. If, then, the administration of large doses of Autolysin is continued at short intervals, the demands put upon the corpuscles in dealing with the proteins thus introduced may exhaust their resources, tending to induce a condition of pernicious anæmia.

The rational procedure in such a case is to discontinue for a time the administration of the protein to which the body has become "immunized"; either giving no treatment at all for a time (days or weeks according to the progress of the case), or else

Digitized by Google

substituting small doses of different proteins. In either case, the dose of the original protein should be small when its use is resumed. Patients who had discontinued the Autolysin treatment for a term of weeks have repeatedly been observed, on resumption of the treatment, to react as vigorously to the small doses as if taking it for the first time.

From all this it will appear that no mere rule of thumb can be applied in determining the dosage, interval of administration, or length of treatment with protein antigens of any individual case of cancer. But a clear recognition of the principles of enzymic response above outlined will furnish the best guide at present available.

In general, it may be said that the dose to be aimed at is that which will carry the red blood count and the haemoglobin test to the normal, and keep the large mononuclear leucocytes in adequate cohorts. More specific reference to the blood conditions, with details as to the all-important differential leucocyte count will be presented in later chapters.

SECTION VII

VEGETABLE PROTEINS IN THE PARENTERAL SYSTEM

It will be recalled that my original interpretation of the action of Autolysin as largely due to its protein content (an interpretation of which the present monograph may be regarded as an elaboration) appeared in the *New York Medical Journal* of October 2, 1915.

In the same number of that Journal, Dr. Beebe referred to the action of the protein content of the extract in the following terms:

"The anaphylactic reaction undoubtedly has its origin in the protein content of the Autolysin and is similar in most respects, though of a milder character, to that produced by the injection of alien animal serum into a sensitized subject . . . . . Autolysin is rich in protein, and a portion of the reaction phenomena is undoubtedly due to this factor. After repeated inoculation some degree of immunity or toleration is required, which expresses itself in a lessened degree of reaction. The local reaction is less marked and the immediate pain of the injection is not troublesome. The feeling of malaise is decidedly milder and the subsequent rise in temperature is not so high with the same sized dose as in the earlier period of treatment. It is wise in most cases gradually to increase the dose until the optimum amount for that patient has been reached. In most cases the best results will be obtained by giving a dose of such size that a

Digitized by Google

mild temperature reaction is produced, but it is not necessary to produce a decided reaction in every case with each injection in order to get good results.

"By repeated intravenous injections it is possible to reach a condition of immunity of such a degree that the anaphylactic reaction either does not occur at all or is much milder."

Dr. Beebe offered no theoretical explanation of the manner of action of the protein, his paper being chiefly concerned with clinical facts. My own treatment of the subject, however, which, bore title of "The Autolysin Treatment of Cancer in the Light of The Proteomorphic Theory," was expressly directed toward an interpretation of the observed facts. As it put forward somewhat in detail a new interpretation of a principle of therapeutic action that is assuming greater importance day by day, it will be worth while here to present part of the interpretation in a direct quotation. It constituted, as far as I am aware, the first attempt ever made to establish the protein response, *per se*, as a therapeutic principle.

An Early Statement of the Autolysin Principle

The presentation in question was sequential to a study of the blood conditions in cancer, which is taken up at another place in the present monograph. The theoretical presentation significant in the present connection is as follows:

The first essential fact as to the composition of Autolysin that must be emphasized and clearly apprehended is that the remedy contains vegetable proteins in solution.

Now vegetable proteins are about the commonest things in the world. We all take quantities of them into our stomachs every day. But taking a protein into the stomach is a quite different thing from having it injected into the circulatory system; and it is believed that the users of Autolysin are the first persons who ever introduced a vegetable protein (excluding of course bacterial proteins) into the human system hypodermically for a therapeutic purpose. [Exception should have been made also of the use of plant pollen in the prevention and treatment of hay fever. I had personally inspected "vaccines" of this character some years earlier (1910) in the laboratory of Sir Almroth Wright, but at the moment of writing I inadvertently overlooked them.] How the agent acts when thus introduced is a question that we shall discuss in a moment. Meanwhile, let it be recalled that the vegetable proteins in question have been extracted from drugs carefully selected because of their non-toxicity.

It is well known that foreign proteins of whatever character, when introduced into the parenteral system, constitute antigens that stimulate the body to the production of defensive enzymes,

Digitized by Google

that tend to proteolyze the antigen itself and to neutralize its toxic products. According to the proteomorphic theory, the chief agents in the production of these proteolytic and antidotal enzymes are the white and red blood corpuscles, the latter being concerned with the end products of the polypeptid order. According to the theory, large numbers of the red corpuscles themselves are destroyed in the liver, in the process of eliminating the toxic end products of protein metabolism from the system. This explains, for example, the pernicious anæmia that may result from the absorption of toxins of protein origin, as in bothriocephalus poisoning.

Similar destruction of the red corpuscles, in their attempt to rid the body of toxins, explains, according to our thesis, the pernicious anæmia that generally accompanies malignant neoplasms. The animal protein cell does not break down without the production of toxic molecules, and wherever animal proteins of any type are being split up parenterally, such destruction of the red corpuscles must occur, with the result that the cytogenic apparatus may finally be overtaxed and find itself unable to keep up the supply.

It seems probable, however, that vegetable proteins, notwithstanding their chemical similarity to animal proteins, are less likely to produce toxic by-products during disintegration. It is a familiar doctrine that animal proteins rather than vegetable are the source of intestinal putrefactions. There is theoretical warrant, according to the proteomorphic theory, for the assumption of the less toxicity of vegetable proteins, in the fact that they doubtless have constituted the food of our ancestors for a much longer period than have animal proteins. Probably the remote ancestors of men were eaters of vegetables for millions of generations before they became eaters of animal foods. And, according to the thesis under discussion, the toxicity of any type of protein is directly proportional to the newness, so to speak, or the infrequency with which the organism has come in contact with it. Toxicity is not a thing per se, but a matter of relativity. Inherently, all proteins are poisonous to every organism except the one producing them. A few drops of eel's blood injected into the veins of a dog will cause death.

But doubtless there is great diversity among vegetable proteins themselves as to the matter of toxicity; and it has already been explained that the drugs selected for the extraction of vegetable proteins in Autolysin were such as are free from any suspicion of harmfulness to the human system. According to the thesis here developed, freedom from toxicity argues a long-established relationship between these particular proteins and the human organism; so it is not surprising that the ones selected

Digitized by Google

include familiar garden plants that have long been under cultivation. Doubtless any number of other plants might have been selected from which vegetable proteins that are effective antigens could have been extracted; but many of them would have introduced, along with their proteins, toxic alkaloids or organic salts or enzymes that would have made them worse than useless.

The result is that the vegetable proteins actually introduced when a hypodermic injection of Autolysin is given, are of a type to produce a minimum of toxicity while at the same time acting as vigorous antigens, stimulating the cytogenic mechanisms to the rapid production of white and red blood corpuscles. Doubtless these corpuscles proteolyze the vegetable protein itself, but in so doing the red corpuscles are not destroyed in large numbers, because they have a minimum of toxic by-products to deal with.

The large mononuclear leucocytes, which have been shown to produce enzymes that are peculiarly active in the splitting up of cancer cells, are usually found to increase very markedly in the blood. There is also increase of the lymphocytes, which are credited with an active share in the splitting up of animal proteins, and of the eosinophiles. The enzymes generated by these protein fighters, begin the disintegration of cancer cells (which, because of their embryonic character are more susceptible to disintegration than are the cells of normal tissue), and the products of such disintegration are liberated into the blood stream, where the red corpuscles, now banded in adequate numbers, continue the work of proteolysis and elimination.

Of course, the disintegrating cancer cells liberate toxic molecules, and in dealing with these the red corpuscles are of necessity destroyed in large numbers in the liver. But this temporary reduction in the numbers of the erythrocytes is compensated almost immediately by the stimulative effects of a succeeding dose of Autolysin, so that unless the breaking down of cancer tissues goes forward very rapidly indeed, the aggregate count of red cells increases from day to day. It is not unusual to find the count above five million, after the Autolysin treatment is well established. The enzyme-forming capacity of the red cells is probably increased proportionately.

The chill and rise of temperature that mark the characteristic reaction to Autolysin, and serve as guides to the clinician, probably mark the period when the cumulative action of the leucocytes has taxed the blood with more polypeptid by-products than the red cells can for the moment handle, so that the ranks of the latter have been momentarily depleted, and the chill gives warning that the system is feeling the effects of toxicity. But the rise of temperature is compensatory, since this in itself stimulates the

Digitized by Google

activity of the cytogenic apparatus, so that in a short time there are usually enough of the corpuscular defenders present to take care of the obnoxious protein products.

If compensation does not take place quickly, the delay serves as a warning to the clinician that he should let a longer interval elapse before giving the next dose of Autolysin, or administer the remedy in smaller doses.

If the foregoing reasoning is accepted, it is clear that we can form a tolerably vivid mental picture of the processes through which the regression of the malignant tumor is brought about under the influence of the vegetable protein antigens that are among the essential constituents of Autolysin. The observed phenomenon of the cessation of pain, which is one of the most uniform and gratifying immediate results of the administration of Autolysin, is explicable as due to the softening and disintegration of the peripheral cancer cells that have encroached upon the nerve fibrils. The time required for the pain-annulling effects to make themselves manifest would appear to depend upon the exact site of the cancer, and the extent to which its cells have involved the nerves. As the cancer tissue steadily regresses, it is withdrawn more and more from interference with the nerves, and the cessation of pain is lasting.

There is very commonly experienced a sensation of gnawing or digging at the site of the tumor, which is not exactly agreeable, but which the patient cheerfully tolerates because he regards it, doubtless quite correctly, as an evidence that salutary changes are taking place within the tissues of the neoplasm.

The cessation of odor in superficial ulcerative neoplasms or in the discharge from uterine or other masses, is readily understood, according to our thesis, as due to the activities of the hitherto depleted but now adequate army of red blood corpuscles. The decomposition products that produce the bad odor are precisely of the character of the protein products that, according to hypothesis, the red blood corpuscles deal with habitually. The odor was, therefore, directly due to the inadequacy of the supply of red blood corpuscles, and it disappears almost as a matter of course when this defect is fully compensated.

All-Importance of the Proteins

It will be clear from the above that very definite ideas were entertained as to the prime importance of the protein content in explaining the therapeutic action of Autolysin.

At the time when the above interpretation was written, we were disposed to feel, however, that a part of the action of Autolysin was due to its non-protein constituents. Definite suggestions were made as to how the chlorophyll in the compound might

Digitized by Google

conceivably act; but it was stated that any hypothesis as to the manner of action of the chlorophyll was put forward only tentatively, and the prime importance ascribed to the protein content was emphasized in a concluding paragraph as follows:

"The provisional explanation of the action of Autolysin as above given, particularly with reference to the share of the vegetable proteins of nontoxic character in stimulating cytogenesis, enables one to form a picture of the physiological processes involved in the regression of cancer under Autolysin treatment that is at least as satisfying as most similar pictures that the therapeutist can elicit regarding the action of any drugs in his equipment. Assuredly the action of Autolysin, as interpreted in the light of the proteomorphic theory, cannot be said to be without scientific foundation. In point of fact, the theory of its action may be said to give substantial support to the confidence of those who have observed with wonderment and gratification its really extraordinary therapeutic action."

It remains now to say that all of the more recent studies at the Beebe-Williams and Clinic have tended strongly to emphasize in our minds the importance of the protein element in the Autolysin compound, and the unessential character of the other constituents. We are still disposed to believe that the chlorophyll bodies in the original Autolysin had a certain effect, but we now think that this effect was largely, if not exclusively, due to their protein content,—for of course the chlorophyll bodies have a protein basis. The fact that all the desired therapeutic effects of Autolysin are secured with the newer form of the remedy, called Special Concentrated Autolysin, from which the chlorophyll has been eliminated, gives strong support to this view.

In general, it may be said that in all the recent experiments with protein antigens conducted by Dr. Beebe and myself, as elsewhere referred to more in detail, we have used the protein content as the gauge for standardization, and as the sole guide to dosage.

Our present conclusion, then, is that the action of Autolysin is to be interpreted in terms of protein antigens, and that the entire experience with Autolysin furnishes the foundation for the establishment of a brand new general principle of therapeutics.

And this brings to mind what I had in view when I said that the history of scientific discovery has few stranger chapters than the one connoting the story of Autolysin. For of course the Autolysin powder, as originally used as a poultice, and as administered in pill form or in a liquid extract taken into the stomach, was used quite without reference to its protein content. In my opinion, such measure of efficacy as the compound had when used locally was due very largely to its incorporation of mustard powder. I very much doubt that it had any efficacy at all as administered by the stomach,—beyond that, possibly, of a very

Digitized by Google

mild tonic and laxative, with no specific effect whatever on malignant growths.

The proteins in the compound, when taken into the stomach, would of course be decompounded, and would have no opportunity to act as parenteral antigens. And of course the application of the powder to a superficial neoplasm, even where there was an open ulcer, would not result in the absorption of protein except to an infinitesimal degree.

So it must be regarded as a sheer coincidence that the saline extract prepared for hypodermic use contained proteins, and hence had efficacy in virtue of the application of a principle in no wise suggested by the original use of the remedy.

Even Dr. Beebe himself did not at first suspect the true character of what had been accomplished. He had observed interesting effects from the local application of the remedy, and he wished to see whether still more striking effects might not be produced if the essential constituents of the powder were extracted and made available for injection directly into the mass of the malignant neoplasm.

Such was the manner of application of the hypodermic extract when first used. It was not at first suspected that the hypodermic extract could be available for the treatment of deep-seated cancers unless some means could be found to inject the remedy directly into their mass. In proof of this, it is recalled that in one case a supra-pubic incision was made into the bladder, in order that local injections of Autolysin might be made into a cancerous mass at the base of the bladder with the aid of a long hypodermic needle specially constructed for the purpose.

Not until very striking results had been attained by the local injections of Autolysin into the substance of superficial neoplasms did the idea suggest itself that conceivably similar results might be attained by introducing the remedy into the general circulation by subcutaneous or intramuscular injection into a distant part of the body.

When this experiment was made, it was found to the astonishment and delight of Dr. Beebe and his associates, that results of a quite unpredicted character were obtained. The remedy appeared to act quite as efficaciously when injected, for example, into the upper arm (the tumor, perhaps, being in the pelvis), as when the extract was brought directly in contact with the cancerous tissue itself.

Then it became evident that we had to do with a remedy having a general, systemic action, operating through the blood stream, and attacking the cancer cells only indirectly.

Finally, the proteomorphic theory was invoked as supplying, seemingly, the most plausible explanation—and, indeed,

Digitized by Google

the only available explanation—of the observed action of the remedy.

Curiously enough it is the mustard seed that supplies the major part of the protein in the extract; yet there is no relation except that of sheer coincidence between that fact and the fact that the mustard gave value to the local application. The mustard oil acted as a local irritant; the mustard protein (globulin) acted as a general antigen. The two actions are totally unrelated, and no one could predict one from knowledge of the other. Yet it was observation of the local effects (not then fully interpreted) that led Dr. Beebe to suggest making the extract, with so remarkable a sequence of results.

The famous story of the discovery of digitalis as the essential ingredient of a shot-gun formula is assuredly far less picturesque and romantic than this story of the isolation of the non-specific protein antigen, opening up a whole new field of therapeutics, from study of a conglomerate mixture of herbs for the most part otherwise inert.

It should be remembered, however, that each of the remaining eleven constituents of the Autolysin powder gives up a modicum of protein, although in some cases (notably that of the quassia, the anthemis, and the colocynth), the amount is so small as to be almost negligible. The total amount of protein extracted from the remaining eight constituents of the product furnishes not far from half the total protein content of the Autolysin extract. In the aggregate, then, the share of these constituents is important, even though the amount of protein supplied by each one is very small. I repeat that all our experiments tend to confirm the conviction that nothing in the nature of these particular vegetable proteins gives them exceptional value as compared with any other vegetable proteins of non-toxic character.

On the other hand, it must be recalled that the main body of evidence as to the value of proteal treatment has been gathered through use of Autolysin, and a long line of further investigation will be necessary before it can be said definitely whether identical results can be attained in the treatment of cancer with other compounds of vegetable proteins or by the use of any single protein, or of the products of partial protein hydrolysis. These, I repeat, are matters regarding which we are not as yet prepared to speak precisely. They are under investigation, as a part of the general study of protein antigens, in the Beebe-Williams Laboratory and Clinic, and we invite the co-operation of the profession at large. Another year of observation must elapse before the experience with the newer proteals can fully match the records already in hand concerning the original proteal mixture.

Digitized by Google

SECTION VIII

THE BLOOD IN CANCER SUBJECTS

It will be recalled by those who have read the original presentation of the Proteomorphic Theory that the theory ascribes to the lymphocytes in the blood the function of beginning the decompounding of protein molecules. It will be recalled also that experiments (of Vaughan) are cited which seem to show that the large monocytes have power to produce enzymes that bring about the decompounding of cancer cells.

It is of pecular interest, then, to inquire as to the modifications of the blood count that are associated with the cancerous condition, and the further modifications that are brought about by therapeutic application of protein antigens.

It has long been recognized by pathologists that there are marked modifications of the blood count in nearly all cases of malignant disease. Most observers have been content to note the reduction of the hæmoglobin index and of the red blood count, and the marked leucocytosis that usually characterizes the condition, at least in its advanced stages. A number of observers, however, have fortunately made more elaborate studies, and records are available in the literature covering a considerable body of cases in which complete blood counts were made that furnished the basis for a comparative study in connection with the original observations that I am about to record.

Dr. Price Jones has published detailed results of the study of 29 cases of cancer, including carcinomas of the breast, stomach, intestine, generative organs, tongue, and larynx, and variously located sarcomata. His results show an average of 3,838,000 red blood cells and 10,409 white cells to the cubic millimeter. The differential count showed 73.7 per cent. of polynuclears, 10.38 per cent. large monocytes, and 13.6 small lymphocytes. Eosinophiles and basophiles are not recorded, but by exclusion are shown in the aggregate to represent 2.32 per cent. of the leucocyte census.

Another interesting series of cases comprises cancer in which there were bone matastases, recorded by different observers, and aggregating 22 cases fully reported. Here the average red blood count was found to be 2,808,000; the average white blood count, 14,214 (increased by the presence of a few cases in which the leucocytosis was extreme). The differential count shows 58.11 per cent. polynuclears; 14.89 per cent. large monocytes; 25.86 per cent. small lymphocytes; 0.87 per cent. eosinophiles; and .027 per cent. basophiles. A considerably modified average is found if we consider only the first count in each of the 22 cases, the result being: red corpuscles, 2,744,000; white corpuscles, 11,500

Digitized by Google

(the aberrant case being omitted); polynuclears, 65 per cent.; large monocytes, 11.7 per cent.; small lymphocytes, 22 per cent.; eosinophiles, 1 per cent.

These results may be compared with the table, herewith presented, of our own untreated cases. It will be seen that there is close general agreement. I would call special attention to the

TABLE III—THE BLOOD COUNT IN CANCER

TWENTY-NINE CASES OF DR. PRICE JONES AT THE MIDDLESEX HOSPITAL, ENGLAND

Nature of Case	No. of Cases	Red Blood Corpuscles	White Blood Corpuscles	Polynuclears	Mononuclears	
					Large	Small
Cancer of the Breast	9	4,230,000	10,400	7,115	1,324	1,661
Carci. of the Stomach	7	3,770,000	9,700	7,070	835	1,598
" of the Intestine	2	4,600,000	14,600	11,478	1,446	1,490
" Generative Organs	5	4,160,000	14,280	10,088	1,671	2,108
" of the Tongue	1	3,780,000	18,600	13,974	1,711	2,845
" of the Larynx	1	2,400,000	6,300	4,365	819	1,091
Sarcoma	4	4,490,000	10,930	7,847	1,158	1,694
Weighted averaged of 29 cases	.....	3,838,000	10,409	7,664 73.7%	1,077 10.38%	1,421 13.6%

TABLE IV—TWENTY-TWO CASES OF CANCER WITH BONE METASTASES REPORTED BY DIFFERENT PHYSICIANS

Observer	Hæmoglobin	Red Blood Corpuscles	White Blood Corpuscles	Polynuclears	Mononuclears		Eosinophiles	Basophiles
					Large	Small		
1. Hawley	75	3,172,000	7,300	63.0	10.0	27.0	0	0
2. Harrington	62	2,751,000	2,500	56.4	20.0	19.6	1.6	0
3. Houston	49	2,300,000	6,700	54.0	9.2	36.2	0.6	0
4. Parkes	...	1,056,000	10,200	78.0	9.5	11.0	1.5	0
5. Harrington	35	1,600,000	14,000	63.0	17.6	16.7	0.7	0
6. Parmentier	60	1,940,000	3,500	60.0	14.0	21.0	4.0	0
7. Wolfer	15	1,550,000	20,000	66.0	12.0	22.0	0	0
8. Kurpjuweit	25	1,825,000	9,100	48.5	31.4	19.2	1.0	0
9. Kurpjuweit	60	4,320,000	19,700	86.1	7.0	6.2	0.7	0
10. Frese	21	900,000	9,220	64.5	19.0	15.0	1.0	0.5
11. Schleip	40	1,984,000	16,400	82.0	3.7	8.2	1.2	0
12. Schleip	105	4,452,000	7,600	58.6	4.6	35.1	0.8	1.6
13. Nægeli	46	2,168,000	6,000	66.0	8.2	19.0	0	0
14. Ward	65	4,760,000	10,800	50.7	17.4	31.2	0.6	0
15. Ward	50	4,920,000	9,000	68.9	6.5	23.3	0.8	0.5
16. Ward	115	4,725,000	3,700	51.0	4.6	42.2	0.4	1.8
17. Ward	85	5,615,000	8,500	68.0	11.4	21.4	0.2	0
18. Ward	56	3,850,000	20,300	60.0	14.0	23.0	3.0	0
19. Kast	...	3,020,000	120,000	96.17	1.25	2.16	0.42	0
20. Turnbull	45	2,150,000	22,000	59.0	8.5	31.0	1.0	0.5
21. Hirschfeld	20	1,000,000	30,000	78.8	15.6	4.6	0.5	0
22. Bloch	50	3,000,000	6,000	56.7	12.7	30.5	0.1	0
	53.3	2,744,000	11,500	65.26	11.7	22.06	1.0	0.2

column showing the percentages of large mononuclear leucocytes. Recalling that in normal blood the large monocytes number only 2 or 3 per cent., as a rule, with perhaps 5 per cent. as maximum, it will be noted that in Price Jones' series of cases these cells number 10.35 per cent. of all leucocytes; in 22 cases of bone metasta-

Digitized by Google

ses, as first counted, they number 11.7 per cent.; in one of our series (26 cases) they number 13.5 per cent., and in another of our series (22 cases) they number 14.05 per cent. It should be understood that the large mononuclear leucocytes do not constitute a homogenous group. They include, in an ordinary cancer case, not only large lymphocytes and normal large monocytes (the macro-

TABLE V—ORIGINAL CASES AT THE BEEBE-WILLIAMS CLINIC

THE BLOOD COUNT IN 26 UNTREATED CASES OF INOPERABLE CANCER

Case No.	Name	Nature of Case	Hæmoglobin	Red Blood Corpuscles	White Blood Corpuscles	Polynuclears	Mononuclears		Eosinophiles	Basophiles
							Large	Small		
346	Mrs. C.	Carci. of Breast	90	4,630,000	9,320	63	12	25	0	0
361	Mr. C.	" " Jaw	90	4,568,000	6,230	77	9.6	13	.3	0
378	Mrs. DeB.	" " Uterus	100	4,272,000	8,000	57	18.3	21.6	3	0
335	Miss D.	" " Breast	80	2,464,000	10,650	70.6	8.6	7.6	2.6	0.3
310	Mr. E.	" " Bladder	65	3,920,000		82	11	6	1	0
394	Mrs. L.	" " Breast	100	5,280,000	9,500	65.5	10	20	4	0.5
349	Mrs. G.	" " Uterus	95	4,564,000	7,700	46.6	13.6	39	.6	0
333	Mrs. H.	" " Breast	85	3,824,000	8,650	50	19	28	3	0
316	Mr. K.	Epithe. of Palate	75	4,096,000	....	61	23	15	1	0
356	Mr. L.	Carci. of Stomach	85	4,640,000	9,880	75.5	12.3	12.3	0	0
375	Miss Mc.	" " Breast	90	3,872,000	7,880	70.6	13.3	14.6	1.3	0
327	Miss M.	" " Mediastinum	90	5,160,000	9,220	64	12.6	21.6	1.6	0
358	Mr. U.	Sarc. of Peritoneum	95	5,272,000	7,550	52.5	20.75	21.5	4.75	0.5
224	Mrs. S.	Epithelioma	95	5,088,000	9,000	78	13	6.5	2.5	0
325	Mr. S.	Carci. of Larynx	85	4,288,000	7,240	77	8	15	0	0
344	Mrs. S.	" " Breast	90	4,684,000	9,220	80.6	12.6	6.6	0	0
362	Mrs. St.	" " Cæcum	85	4,016,000	8,100	71.3	13	15	0	0.6
331	Mr. S.	Mixed Parotid Cancer	70	3,744,000	9,780	67	10	23	0	0
312	Mrs. Y.	Carci. of Uterus	45	2,730,000	16,600	66	16	16	2	0
355	Mrs. S.	" " Intestine	85	3,376,000	8,660	74.3	14.3	10.3	1.3	0
	Mr. M.	Doubtful Diagnosis	45	1,424,000	11,550	68	8	22	2	0
341	Mr. G.	Carci. of Uterus	90	5,360,000	8,480	57	20	21.5	1.5	0
	Dr. L.		100	4,096,000	10,000	67	13.5	9.5	10	0
	Dr. Mc G.					79.3	9	6.6	4.6	0
	Mr. P.	Ep. of Tongue	95	4,992,000	9,800	62	9	22	7	0
339	Mrs. T.	Carci. of Stomach	85	4,920,000	9,680	53.3	21.3	25	0.3	0
Average for above 26 cases			84.4	4,258,000	9,240	67.5	13.5	17	2	.07
Average for 22 cases in Table VI			81.9	4,271,000	8,840	67.95	14.05	16	1.69	.07
Weighted averages for 48 cases			83.2	4,264,000	9,080	67.72	13.77	16.6	1.8	.07
Unweighted " " 99 "			73.2	3,777,000	10,000	68.6	12.45	17.16	1.56	.11

The above 26 blood counts of cases of inoperable cancer constitute a fairly representative group, presented here together because they chance to be cases in which only a single blood count was made. They are otherwise unselected. The averages of this group may advantageously be compared with those of a second group of untreated cases detailed in Table VI. A combination of these charts gives the averages for 48 untreated cases of inoperable cancer. For purposes of comparison, the averages of the 29 cases of Price Jones and the 22 cases of bone metastases reported by various investigators are also presented. It will be seen that there is close general agreement. The relatively low red corpuscle count in the bone cases may perhaps be due in part to direct involvement of the marrow. The Price Jones cases were hospital cases. The Beebe-Williams cases were ambulatory, although late stage inoperables. Thus we have a fairly representative group of 99 cases, and, in so far as any generalizations are justified from so small a number, we may take the grand average as suggesting a typical blood picture in advanced stages of the cancerous condition.

phages of Metchnikoff), but myelocytes (neutrophile, eosinophile, and occasionally basophile), leucoblasts, and lymphoidocytes. For the moment, however, it will be convenient to group all of these together, in consideration of their probable similarity of origin, and their obvious similarity of structure.

Digitized by Google

Striking the (unweighed) average for these 99 cases, we find the large mononuclears (of these various groups) aggregated to represent 12.45 per cent. of the total leucocyte count. This is about two and a half times the normal maximum percentage; and it would appear that we may accept some such modification as this of the large monocyte count as typical of advanced cases of malignant neoplasms. Individual cases, as a matter of course, show exceptions, but there appear not to be more than five or six cases in the entire 99 in which the count of large monocytes was found as low as the normal maximum limit.

We are justified, then, I think, in regarding a marked increase of the large monocytes as a typical manifestation of the presence of malignant neoplasms in an advanced stage. These clinical observations in the human subject find support, it may be added, in Price Jones' observations of cancerous mice in which also a very marked increase of the large monocytes was noted. It should be observed, however, as having interest in another connection, that the percentage of large monocytes in the blood of the normal mouse is far higher than in the human subject. The figures given by Price Jones are, for normal mice, 21.5 per cent.; for cancerous mice 32.2 per cent. of the total leucocyte count.

The question at once arises as to whether the observed increase of large monocytes in the cancerous condition is to be regarded as a part of the disease process, or whether, on the other hand, it manifests a salutary modification indicating nature's attempt to combat the invasion of the lawless cancer cells.

In view of the known functions of the leucocytes in guarding the body against bacterial invasions, we may, I think, unhesitatingly accept the increase of leucocytes in general in the cancerous condition, and of the large monocytes in particular, as representing a salutary process. The fact that Vaughan's experiments showed that enzymes produced by the large monocytes bring about at least partial decompounding of cancer cells naturally comes to mind in considering the observed fact of the increase of these monocytes in the cancer subject.

It seems at least a justifiable inference that the presence of the cancer cells has directly stimulated the production of large monocytes, just as the presence of foreign pathogenic bacteria stimulates the increased production of phagocytic polymorphs.

If this view is accepted, it is permissable to suppose that in a very large number of cases incipient malignant neoplasms are nipped in the bud, so to speak, by the activities of the large monocytes; and that the presence of a tangible cancer demonstrates the fact that, in this individual case, the body has been unable to produce the defending corpuscles in adequate numbers to overmaster the invading cancer cells; although, at the same time, it must be

Digitized by Google

observed that the presence of the increased number of monocytes shows that the bodily organism has not given up the fight.

It is this view that is to be borne in mind in connection with the observed modification of the blood count brought about by the administration of protein antigens, to which we now turn.

The Blood Count as Modified by Protein Antigens

When charts made at the Beebe-Williams Clinic, showing the results of such blood counts in about 150 original cases were available, it was at once evident that there were very striking and characteristic modifications of the differential count coincident with the administration of the vegetable proteins; and that these were curiously similar to changes coincident with the administration of Dr. Beebe's anti-thyroid serum.

A typical, yet somewhat extreme, case, for example, was that of a patient suffering from carcinoma of the throat whose blood on the 8th of October, 1915, at an early stage of the Autolysin treatment showed 7.3 per cent. of large mononuclears to 18 per cent. of small ones; and whose count about six weeks later (on the 22nd of November) was almost precisely reversed as regards these particular elements, showing 18.3 per cent. of large mononuclears to 7.6 per cent. of small ones.

Other specific cases show the proportion between large and small mononuclears as follows: 19 to 20.6 at an early stage of treatment and 34 to 11.5 at a later stage; 14 to 31.6 at an early stage, and 27.75 to 15 at a later stage; 9 to 16 at an early stage, and 21.5 to 8 at a later stage; and 10.5 to 29 at an early stage, against 31 to 15.5 after three months of Autolysin treatment.

A typical thyroid case showed the balance between large and small mononuclears as 8 to 19.6 on the 12th of October, and shifted to 25 to 19.5 on the 17th of December, after two months of use of anti-thyroid serum.

Reverting to Vaughan's experiment in the inoculation of sheep with the ground cancer tissue, in the light of these observations, it seems a fair inference that, since vegetable proteins on one hand and anti-thyroid sheep serum on the other produce precisely the same results in human subjects that Vaughan observed in case of the sheep inoculated with cancer tissue, the principle involved is the response to the protein antigen as such rather than a specific response to any particular type of protein.

This, it will be observed, would be fully in keeping with the assumption that the mononuclear leucocytes are the agents chiefly involved in beginning the decompounding of foreign proteins in general when brought in contact with the blood.

Be the theoretical explantion what it may, however, the thing that has peculiar significance in the present connection is the ob-

Digitized by Google

served fact that the hypodermic administration of proteins (independent of any other treatment) has been demonstrated to bring about a very marked modification of the leucocyte count, in the direction of the increase of the large mononuclears. For the moment we may disregard questions as to the distribution of different types of monocytes, considering the group of large single-nuclear leucocytes as an entity. More detailed analysis will be made in another connection, but if introduced here might obscure what appears to be an important and hitherto unrecognized principle of leucocytic response to the stimulus of proteins.

As regards the total leucocyte count, this is sometimes increased rather markedly under the protein treatment. Dr. Beebe called attention to this in his paper of October 2, 1915, referring also to certain other aspects of modifications of the blood count, in the following words:

"In a considerable percentage of cases a marked leucocytosis follows the injections, accompanied by relatively large lymphocytosis. Such a blood change does not occur to a large degree in every patient, but some of the most striking improvements have occurred in patients whose total leucocyte count has gone as high as 20,000 to 30,000 with a relative proportion of thirty per cent. to fifty per cent. lymphocytes. The red blood cells likewise increase in number. There has been a sufficient stimulation of the blood forming organs to produce occasionally the appearance of myelocytes in the blood and in some instances a marked eosinophilia. The writer has seen patients with from six to eighteen per cent. of eosinophiles in a total blood count of 15,000 to 25,000."

More extended experience, however, tends to the conclusion that so pronounced a leucocytosis under the influence of protein antigens is exceptional, and that as a rule the total white count, if in the beginning excessive, is rather modified in the direction of reduction when the case progresses favorably under the proteal treatment. So far as a general statement is justifiable from the number of cases under observation, it would seem that the most important transformation is that concerned with the stimulation of production of large monocytes. Cases in which no favorable modifications of this kind have taken place under proteal treatment have not been observed to make favorable clinical progress.

Fairly typical of desired results is case number 348, who on the 15th of October (before beginning treatment) had a hæmoglobin index of 80 per cent., a red count of 3,168,000, a white count of 9,880; with 78.6 poly., 10.6 large monocytes and 8.3 small lymphocytes; and who on the 1st of December showed a hæmoglobin index of 90 per cent., a red count of 4,944,000, and a white count of 7,500; with 66.5 per cent. poly., 21 per cent. large monocytes, and 10 per cent. small lymphocytes.

Digitized by Google

TABLE VI—ORIGINAL CASES AT THE BEEBE-WILLIAMS CLINIC

Blood Count in 22 Cases of Inoperable Cancer Before Treatment

Case No.	Name	Nature of Case	Hæmoglobin	Red Blood Corpuscles	White Blood Corpuscles	Polynuclears	Mononuclears		Eosinophiles	Basophiles
							Large	Small		
369	Mrs. B.	Carci. of Breast	90–95	4,480,000	8,220	51	14	31.6	2.6	.6
368	Mrs. C.	" " "	90	3,976,000	9,330	65.6	14.3	17.3	2.3	.3
360	Mr. D.	Epithe. of Jaw	90	3,776,000	7,880	51	17.5	23.5	7.75	.25
345	Mr. D.	Carci. of Larynx	90	4,668,000	8,350	79	15	6	0	0
309	Dr. G.	Sarc. Abdomen	...	5,056,000	....	75	17	6	2	0
381	Mrs. H.	Melanoma	100	4,752,000	7,600	80.5	7.6	8.6	3.3	0
313	Mrs. K.	Carci. of Breast	90	4,960,000	....	61.5	23.5	14	1	0
354	Mrs. M.	" " "	95	5,064,000	8,150	73.3	12.6	13	1	0
359	Mrs. Mc.	" " "	90	3,608,000	9,100	63.6	16.3	18	2	0
322	Mr. N.	Epithe. of Face	60	3,212,000	....	74	9	17	0	0
371	Miss N.	Carci. of Breast	90–95	4,456,000	7,900	65	15.6	16.3	3	0
332	Miss V.	" " "	85	5,008,000	8,880	64	16	24	0	0
317	Miss W.	" " "	85	4,137,000	....	66.6	14.3	20.6	.6	.6
348	Mr. E.	" " Stomach	80	3,168,000	9,880	78.6	10.6	8.3	2.3	0
314	Mr. Mc.	Epithe. of Mouth	90	4,704,000	5,250	74	15	11	0	0
376	Mrs. T.	Car. Gall Bladder	85	4,600,000	8,300	70.3	12	15.2	2	0.3
301	Mrs. B.	Carci. of Larynx	80	4,200,000	....	48	18	31	0	0
348	Mr. E.	" " Stomach	80	3,168,000	9,880	78.6	10	8.3	2.3	0
287	Mr. H.	Sarc. of Testicle	80	3,592,000	13,500	81.6	7	11.3	0	0
399	Mrs. M.	Carci. of Breast	95	5,120,000	9,300	75.5	15	8.5	1	0
374	Mr. T.	Sarc. of Jaw	85	4,130,000	10,000	53.6	15.6	23.3	3.3	0.3
317	Miss W.	Carc. of Breast	85	4,137,000	....	63.6	14.3	20.6	0.6	0.6
	Average		81.9	4,271,000	8,840	67.95	14.05	16	1.69	.07

The Same 22 Cases After an Average Period of 41 Days of Autolysin Treatment

Case No.	Name	Nature of Case	No. of Days	Hæmoglobin	Red Blood Corpuscles	White Blood Corpuscles	Polynuclears	Mononuclears		Eosinophiles	Basophiles
								Large	Small		
369	Mrs. B.	Carci. of Breast	21	100	5,724,000	6,500	45.3	32	18.3	3	1.3
368	Mrs. C.	" " "	29	95	4,112,000	8,500	64.6	19	12.3	3.6	.3
360	Mr. D.	Ep. of Jaw	39	95	4,384,000	6,600	52.6	17.3	20.6	9	.3
345	Mr. D.	Carci. of Larynx	21	90	4,720,000	7,880	73	16.6	5	4.6	0
309	Dr. G.	Sarc. of Abdomen	14	...	3,412,000	7,850	59	22.5	16	2.5	0
381	Mrs. H.	Melanoma	30	100	4,500,000	8,200	81	12.5	5	1	.5
313	Mrs. K.	Carci. of Breast	80	100	5,564,000	8,000	60	19.3	17.3	3.3	0
354	Mrs. M.	" " "	73	100	5,500,000	7,800	60	23	14	2	1
359	Mrs. Mc.	" " "	57	100	4,384,000	7,200	59	16.5	19	4.5	.5
322	Mr. N.	Ep. of Face	74	85	4,192,000	7,700	51.5	19.5	26.5	2.5	0
371	Miss N.	Carci. of Breast	34	95	4,352,000	8,600	59.5	16.5	21	3	0
332	Miss V.	" " "	90	100	5,656,000	8,900	48.5	27	20.5	4	0
317	Miss W.	" " "	38	85	4,944,000	7,330	56.6	21	18.6	3.6	.3
348	Mr. E.	" " Stomach	47	90	4,944,000	7,500	66.5	21	10	2.5	0
314	Mr. Mc.	Ep. of Mouth	31	85	4,888,000	8,650	68.3	19.3	11.6	.6	0
376	Mrs. T.	C. Gall Bladder	62	100	4,896,000	9,600	62	15.5	19.5	2.0	0
301	Mrs. B.	Carci. of Larynx	32	90	3,724,000	7,270	75	14	11	0	0
348	Mr. E.	" " Stomach	48	90	4,944,000	7,500	66.5	21	10	2.5	0
287	Mr. H.	Sarc. of Testicle	4	85	3,256,000	8,500	73	12.3	14.0	0.6	0
399	Mrs. M.	Carci. of Breast	8	100	4,896,000	9,500	69.5	14.5	13.5	1.5	0
374	Mr. T.	Sarc. of Jaw	32	95	4,864,000	8,300	70.5	18.	6.	5.5	0
317	Miss W.	Carci. of Breast	35	85	4,944,000	7,330	56	21	18.6	3.3	0.3
	Average		40.4	93.5	4,667,000	8,000	62.6	19.05	14.94	2.95	0.2

Modification of the blood count following the administration of fairly vigorous Autolysin treatment. Particular attention is called to the notable increase in the large mononuclears. Such a modification is certainly one of the most characteristic, and perhaps the most important, of the changes brought about by the proteal treatment. Note also the increase in hæmoglobin and in red corpuscles, and the decrease in white corpuscles as a whole and in the percentage of polynuclears.

These cases are grouped together simply because they are cases in which an original blood count, made before treatment, was supplemented by a subsequent count after treatment. They are otherwise quite unselected, and are strictly comparable to the cases shown in the earlier chart. The blood picture of the treated cases shows wide departure from the type-picture supplied by the 99 untreated cases.

Digitized by Google

The average results of fourteen unselected cases under the protein treatment are summarized thus: At the beginning of treatment hæmoglobin index 89 per cent., red corpuscles 4,500,000, white blood corpuscles 8,878; with 68 per cent. polymorphs; 14.9 per cent. large monocytes; 14 per cent. small lymphocytes; .65 per cent. eosinophiles; and 0.32 basophiles. At a later stage after an average of 42 days of protein treatment, hæmoglobin index 96 per cent.; red corpuscles 4,930,000, and white blood corpuscles 8,107; with 62 per cent. polymorphs; 18 per cent. large monocytes; and 16 per cent. small lymphocytes; 3 per cent. eosinophiles; and 0.35 basophiles.

Groups of cases from which similar averages are computed make up the accompanying tables. They appear to justify the belief that modifications of the blood count of a very definite character are superinduced by the administration of Autolysin, and that these changes give support in very emphatic measure to the proteomorphic thesis as to the activities of the white and red corpuscles in dealing with foreign proteins.

New Laboratory Evidence for the Proteomorphic Theory

The subject is so important that it may be of interest to call attention here to two items of new knowledge that give support to the proteomorphic hypothesis as to the actions of the blood corpuscles.

One line of work that may be cited in this connection refers to the presence of uric acid in the red corpuscles. In the *Journal of Biological Chemistry,* August 20, 1915, Benedict shows that uric acid exists in the blood in two forms, in a "free" and in a "combined." Ox-blood which, when tested by the method of Folin, hitherto considered reliable, showed a content of 0.2 mgm. of uric acid per 100 c.mm., was found as a rule to contain in reality about 7. mgm. of total uric acid per 100 c.c. of blood, practically all of this being contained in the red blood cells. "If the ox blood were allowed to stand at room temperature and protected from bacterial contamination, there was found to take place a gradual transition from the combination to the free form of uric acid, apparently due to the action of some ferment. . . . . Benedict suggests that possibly the free uric acid is that which is ready for excretion as such, while the combined is capable of further catabolism." (Summary appearing in *Medical Record.*)

It must be obvious that this finding of large quantities of uric acid in the red cells gives strong support to that part of the proteomorphic theory which postulates the red cells as the seat of the enzymic activities which accomplish the ultimate decompounding of the protein by-products. Uric acid is one of the most important of these by-products. It chances to be one that can ulti-

Digitized by Google

mately be eliminated by way of the kidneys; but whether the red cells excrete it into the blood for that purpose, or whether it merely is left in the blood stream when the red cell is disintegrated in the liver, is still conjectural. Meantime Benedict's experiments give additional evidence that the red cells have precisely such enzymic functions in connection with the later stages of decompounding of the protein molecule as the proteomorphic theory postulates.

Possibly a few words of further exposition and interpretation may be desirable, illustrating a little more in detail the chemical aspects of the observed facts in connection with the suggested explanation along the lines of the proteomorphic theory.

Note, then, that the chemical formula of uric acid is $C_5H_4N_4O_3$. Obviously we have here a substance not distantly related to some of the amino-acids, but proportionally richer in nitrogen than any one of these, the only one approaching it in this regard being arginine ($C_6H_{14}N_4O_2$). Another significant distinction between uric acid and amino-acid is the fact that it contains three atoms of oxygen and only four atoms of hydrogen. There is no animo-acid with less than five atoms of hydrogen; and all but three of them have either two or four atoms of oxygen, each of the three exceptional ones having only a single atom of nitrogen.

We have, then, in uric acid a compound relatively rich in nitrogen and oxygen but poor in hydrogen. To modify it by adding a molecule of water would probably (in view of the four atoms of oxygen) give it extreme instability; and to take a molecule of water away from it would deplete its hydrogen supply, which is already below the minimum amino-acid standard. Uric acid, therefore, appears to represent an end product of the split protein molecule of such structure that it does not afford available material for the making of amino-acids—the only form of nitrogenous building material that the system can utilize in its synthetic operation. This applies, at any rate, to the portion of uric acid which finally appears in the blood plasma. The red blood corpuscle does, apparently, modify a part of the original uric acid supply, since only a fraction of it appears in the plasma. Incidentally, we may note that the capacity of the red blood corpuscle to make such modification, coupled with the fact that the proteal treatment increases the supply of red blood corpuscles, may explain, in part at any rate, the observed value of proteals in the treatment of rheumatoid affections.

Similar reasoning applies, seemingly, to those other waste-products of proteal metabolism, urea (CH_4N_2O) and bilurubin ($C_{16}H_{18}N_2O_3$); each with an odd number of oxygen atoms; one hopelessly deficient in carbon atoms, the other with an excess of

Digitized by Google

them. The genesis of urea is not very clearly established; but the origin of bilurubin as a product of the destruction of red corpuscles in the liver has long been known; and as a matter of course, it received consideration in the development of one important aspect of the proteomorphic theory. That the observations linking uric acid with the red corpuscles were made subsequently to the putting forth of the proteomorphic theory, and quite independently, gives them added value as corroborative of the truth of the theory itself.

Quite different in character, but no less interesting and suggestive in the present connection, are certain experiments recorded by Drs. M. W. Manwaring and Yoshio Kusama, of the Department of Bacteriology and Immunity of Leland Stanford, Jr. University, as recorded in the *Proceedings* of the Society for Experimental Biology and Medicine, of May 24, 1916. These experiments go to show that the blood corpuscles of a rabbit actively absorb goat serum proteins, whether the goat serum is mixed with the (defibrinated) rabbit's blood in a receptacle outside the body or whether it is injected into the system of the living rabbit.

This observation, obviously, gives the strongest support to the assumption of the proteomorphic theory that the blood corpuscles are the agents chiefly concerned in dealing with foreign proteins; the assumption that forms the chief basis for the explanation of the therapeutic action of the proteal remedies with which the present monograph is concerned.

It should be added that, in the experiments just cited, it is further recorded that about 25 per cent. of the goat protein may remain in the rabbit's blood serum. "If the serum and corpuscle fractions (of the blood), are allowed to undergo independent autolysis (10 hrs., 37° C.) a distinct restoration of the goat protein is observed in each fraction. The restoration of the protein in the corpuscle fraction, however, is usually much more pronounced than that in the serum fraction, and may amount to as much as 50 per cent. of the total protein originally added to the blood."

From this it would appear that something like 25 per cent. of the goat serum originally injected is unrecovered, presumably having been hydrolyzed to a stage of decomposition at which it is no longer recognized as goat protein.

It would appear to be a logical inference that such hydrolysis of the goat serum proteins has been effected by enzymes generated in the bodies of the corpuscles which, according to the observations of the experimenters, constituted the chief medium for absorption of the foreign proteins. As far as they go, these experiments afford direct collaboration of one of the principle theses of the proteomorphic theory.

Digitized by Google

Possibly it may seem surprising that so large a proportion of the goat serum proteins remained unhydrolyzed after 10 hours maceration. It must be obvious, however, that corpuscles undergoing autolysis outside the body may have far less enzymic activity than they would exhibit under normal conditions. But in addition to this it should be observed that the amount of goat serum introduced in these experiments was enormously large as contrasted with any doses of foreign protein administered therapeutically to the human subject, amounting, in fact, to one per cent. of the rabbit's blood. Assuming that the goat serum comprises at least 20 per cent. of proteins, the amount of foreign protein thus introduced would constitute one-fifth of one per cent. of the total bulk of the rabbit's blood.

That the corpuscles of the rabbit's blood were able to absorb at least 50 per cent. of this shows remarkable capacity on the part of the corpuscles for handling foreign proteins that invade the medium in which they lie.

But it will be recalled that the normal proteals under discussion in this monograph contain only 3 mgm. of nitrogen to the cubic centimeter, or the equivalent of less than 2 per cent. of vegetable proteins. Meantime the amount of this 2 per cent. solution of proteins used in a hypodermic dose is only one or two cubic centimeters, as a rule; and almost never more than 3 or 4 cubic centimeters. Such a dose, introduced into the large quantity of blood in the human body, obviously constitutes an infinitesimal protein intrusion in comparison with the one per cent. of goat serum mixed with the rabbit blood in the experiments of Manwaring and Kusama.

Since these experiments now give us an inkling of the capacity of the blood corpuscle, the thought not unnaturally suggests itself that possibly we have hitherto used proteals in much smaller doses than might be permissable or advantageous. Here, obviously, is an interesting field for future experimentation, in connection with cancer cases that have proved intractable to the proteal medication as hitherto administered. It must be recalled, however, that it has been customary to carry the dosage to the point of producing an anaphylactic response, and that with most patients this is likely to occur with a dose of thirty minims or less of a two per cent. protein solution. On the other hand, in some early tests that antedated the beginning of proteal therapy, Dr. Beebe administered doses of one hundred cubic centimeters of sheep-blood serum into the peritoneal cavity of a cancer patient, with seemingly beneficial results. It is noteworthy that the severity of the deferred anaphylactic reaction (including chill) is by no means determined exclusively by the quantity of protein administered. It has already been noted that proteins to which the system has not been habit-

Digitized by Google

uated, such as that of alfalfa, produce relatively strong reaction. Moreover, it has been observed that an extract of the Autolysin powder made by boiling (in which proteoses are largely present), gives very marked reactions when administered even in very small doses. Questions as to the relative merits of proteoses, peptones, and polypeptids, as compared with unbroken proteins, await further investigation.

Some Practical Hints

Meantime let me offer a brief further interpretation of the blood count modifications as bearing on the practicalities of the proteal treatment, when applied to various types of cancer in divers stages of progress, in accordance with our antecedent experience.

It is almost axiomatic to say that observation of the blood count must in future be regarded as indispensable as a guide to dosage and frequency of administration in carrying out the proteal treatment of cancer. This is particularly true, however, after treatment has been continued for a period of five or six weeks.

Up to that time, there is almost certain to be favorable progress of the case if the remedy is pressed pretty actively from the outset, the doses being carried to the point of securing a pronounced general reaction on at least one occasion, and subsequently modified so that there is a mild reaction.

During this stage, there will usually be observed a pronounced increase of red blood corpuscles; but this is no more notable than the lymphocytosis, with marked preponderance of the large cells.

It should be observed, however, that the activities of the monocytes in beginning the decompounding of cancer cells may be so great as to put so severe a tax on the energies of the red blood corpuscles that their numbers will be for a time materially reduced, even when the case is progressing favorably.

A very good illustration of this is furnished by case 309, in which there was a large abdominal sarcoma located near the spine, which had been declared irremovable after an exploratory incision. On the 19th of September, 1915, two days after beginning the Autolysin treatment, this patient showed a red blood count of 5,066,000; with 75 per cent. polymorphs, 17 per cent. large monocytes; 6 per cent. small lymphocytes and 2 per cent. eosinophiles. Two weeks later the red blood count had decreased 3,412,000; but in the meantime the polynuclears had decreased to 59 per cent.; there being now 22.5 per cent. large monocytes, 16 per cent. small lymphocytes, and 2.5 per cent. eosinophiles.

Taken by itself, the decrease in red blood corpuscles might seem alarming; but that the above interpretation of this decrease is correct is suggested by the fact that the patient went ahead stead-

Digitized by Google

ily and rapidly to clinical recovery with apparent entire regression and disappearance of the tumor, so far as could be determined by palpation. The case was supposed to be hopeless by the surgeon who attempted the operation; yet progress was so spectacular under the Autolysin treatment (exclusively) that a few weeks later the patient returned to his home and took up once more his accustomed work as a practicing physician.

Such a reduction in the red blood corpuscles under the Autolysin treatment as that just noted would be regarded with equinimity, however, only where there was, as in the instance cited, a large tumor mass undergoing rapid disintegration. And even then, it is questionable whether, as a rule, it would be desirable to carry forward the disintegration of the tumor mass so rapidly as to produce a marked reduction in the red blood corpuscles. A better way, ordinarily, would be to regulate the dosage so as to secure only such amount of hydrolysis of cancer cells as can be dealt with by the red blood corpuscles without reducing their ranks much below the five-million mark.

Cases are reported where the dosage of Autolysin was pressed so actively from the outset that the breaking down of a pelvic cancer was effected so rapidly that the system could hardly have been expected to withstand the shock had there not been opportunity for exterior discharge and drainage. One physician described the results attained in such a case as reminding him of the effects of a curette, so rapid was the removal by exfoliation of the cancer tissue.

In such a case, there is obvious danger of severe hemorrhage. This danger would be obviated, at least in a measure, if the dosage were so regulated that the decompounding of the cancer cells was less rapid.

I have elsewhere pointed out that the critical period in the treatment of Autolysin cases comes after an interval of several weeks, when the systemic response has been carried to the maximum. Almost invariably, the question then arises as to the best manner of continuing treatment, in order that the effects may be cumulative, and the case carried to the favorable termination that seemed promised by the early response.

It is now that constant appeal should be made to the microscope to determine the precise status of the red blood corpuscles and the various leucocytes. An endeavor should be made to keep the former as near as possible to the five-million mark; while it is to be hoped that the lymphocytes will continue to represent at least one-third of the leucocyte count, and that the large mononuclears will outnumber the small ones.

A typical satisfactory blood count is shown by patient number 239 (carcinoma of the breast), whose blood on the 8th of Janu-

Digitized by Google

ary, 1916, after about six months' treatment, showed 100 per cent. hæmoglobin, 5,096,000 red blood corpuscles, and 8,000 leucocytes with 60 per cent. polys., 23.5 large monocytes; 13 per cent. small lymphocytes; 2.5 eosinophiles, and 1 per cent. basophiles.

At the time when this count was made, the patient was steadily progressing, and she went ahead to seemingly complete clinical recovery.

TABLE VII—ORIGINAL CASES AT THE BEEBE-WILLIAMS CLINIC

THIRTY-ONE UNSELECTED CASES OF INOPERABLE CANCER AT EARLIER AND LATER STAGES OF PROTEIN TREATMENT

FIRST COUNT AFTER AN AVERAGE PERIOD OF NINETY DAYS OF TREATMENT

Case No.	Nature	Nature of Case	No. of Days	Hæmoglobin	Red Blood Corpuscles	White Blood Corpuscles	Polynuclears	Mononuclears		Eosinophiles	Basophiles
								Large	Small		
294	Dr. A.	Ep. of Tongue	43	95	4,864,000	7,330	74.6	7.3	18	0	0
366	Sr. A.	C. of Breast	106	95	4,448,000	8,200	66	13.5	16	3.75	.5
278	Mrs. B.	" "	105	90	4,400,000	..	58.6	19	20.6	1.6	0
16	Miss D.	" "	123	90	4,464,000	..	59	17	24	0	0
153	Mrs. G.	" Uterus	87	88	4,656,000	..	73	13	12	0	0
263	Mrs. H.	" "	126	90	3,744,000	7,500	58	20	20	2	0
270	Mrs. H.	" Breast	5	...	....	..	73	17	9	1	0
94	Mrs. H.	Ep. Forehead	190	95	5,160,000	8,800	55	26	14	4.5	.5
233	Mrs. L.	C. of Breast	28	...	4,680,000	..	65	19.5	15	.5	0
239	Mrs. M.	" "	141	90	3,376,000	7,200	64.3	16.3	15.6	3.6	0
131	Mrs. N.	" Uterus	171	100	5,964,000	7,600	62	18.6	18.3	1	0
258	Mrs. N.	" Breast	47	90	5,330,000	..	59	18	23	0	0
248	Mr. O.	Sarc. of Test	72	85	4,352,000	..	71	9	16	.3	0
235	Mr. P.	C. of Jaw	65	...	4,352,000	..	68.3	14	9	4	0
64	Mr. P.	Ep. of Cheek	115	80	4,240,000	..	72	9.5	18.5	0	0
149	Mrs. R.	C. of Breast	79	86	4,570,000	..	63.5	21	15.5	0	0
370	Mrs. R.	" Skin	5	95	4,896,000	10,200	72.6	14	10.6	2.6	0
84	Miss R.	Chond-Sarc	170	95	5,128,000	10,200	71.75	11.5	16.25	.5	0
289	Mrs. S.	C. of Breast	38	90	4,616,000	..	51.5	20	25	3.5	0
242	Mrs. S.	Ep. of Face	69	75	2,800,000	..	60	10.5	29	.5	0
138	Mrs. F. S.	Sarc. of Phar	129	85	3,554,000	9,000	56.3	17	24.3	2.3	0
168	Mrs. S.	C. of Breast	21	75	4,226,000	..	65	20	15	0	0
347	Mrs. S.	" "	90	75	4,280,000	8,440	42	28	30	0	0
193	Mr. S.	" Jaw	165	100	3,936,000	7,600	53	19.5	20	1.5	0
280	Mrs. S.	" Thyroid	159	100	4,460,000	7,200	74	15.6	6.6	4	0
296	Mr. Von E.	Sarc. of Leg	24	90	4,730,000	..	54	20	26	0	0
23	Miss W.	C. of Breast	124	80	4,440,000	..	60	13	27	0	0
168	Miss W.	" "	88	80	4,448,000	..	66.3	11.6	20	2	0
251	Mrs. W.	" "	63	85	3,570,000	..	74	11	11	4	0
189	Mr. M.	" Rectum	83	80	4,312,000	..	77.6	11.6	10.6	0.6	0
391	Mrs. W.	" Ovary	60	100	4,116,000	8,800	52.0	25.5	14	8.0	.5
	Average		90	88.5	4,400,000	8,270	63.69	16.37	17.72	1.7	.05

This table may advantageously be compared with earlier tables showing blood condition in untreated cancer cases, and with the table on the opposite page, showing later history of the same cases.

It will be of interest to contrast this blood count with another, No. 399, which chanced to be made on the same day, in which the hæmoglobin test was also 100 per cent. and in which the red blood count was 4,896,000, but in which the leucocyte count was 9,500 (more than could be desired), polymorphs representing 69.5 per cent., and large monocytes, only 14.5 per cent., as against 14.5 per cent. small lymphocytes, together with 1.5 per cent. eosinophiles and 1 per cent. basophiles.

Digitized by Google

Here, it will be observed, there is substantial uniformity between the two counts except as regards three factors: namely (1) the total leucocyte count, which was 9,500 in the second patient against 8,000 in the first; (2) the polynuclear count, which was 59.5 against 60; and (3) the large monocyte count which was 4.5 against 23.5. These differences, however, are highly significant, in view of the sutdies of the blood count above outlined.

TABLE VIII—ORIGINAL CASES AT THE BEEBE-WILLIAMS CLINIC

THE SAME 31 UNSELECTED CASES AFTER AN AVERAGE OF 152 DAYS OF PROTEIN TREATMENT

Case No.	Name	Nature of Case	No. of Days	Hemoglobin	Red Blood Corpuscles	White Blood Corpuscles	Polynuclears	Mononuclears		Eosinophiles	Basophiles
								Large	Small		
94	Dr. A.....	Ep. of Tongue.....	87	90	5,288,000	9,800	73	18.3	7.6	2.6	1
36	Sr. A.....	C. of Breast.....	134	100	4,160,000	6,700	48	26	24.5	1.5	0
78	Mrs. B....	" " "	193	100	4,832,000	6,100	54.5	34	11.5	0	0
16	Miss D....	" " "	215	100	5,252,000	7,500	61.5	13	24	1.5	0
53	Mrs. G....	" " Uterus.....	170	90	3,840,000	7,500	55	22	20.5	2.5	0
33	Mrs. H....	" " "	142	100	3,424,000	7,700	72.5	10	15.5	2	0
70	Mrs. H....	" " Breast.....	122	95	5,696,000	6,800	72.5	17.5	5.5	4	0
04	Mrs. H....	Ep. Forehead.....	209	95	5,240,000	8,000	58.5	18	21.5	2	0
38	Mrs. L....	C. of Breast.....	165	100	5,652,000	8,600	76.5	13.5	8.5	1	.5
29	Mrs. M....	" " "	172	100	5,096,000	8,000	60	23.5	13	2.5	1
31	Mrs. N....	" " Uterus.....	207	95	5,124,000	8,300	62	20.5	16.0	1.5	0
58	Mrs. N....	" " Breast.....	150	100	4,800,000	9,400	58.5	26.5	13.5	1.5	
58	Mr. O.....	Sarc. Testicle.....	162	90	5,404,000	8,300	71.5	20.5	8	0	0
55	Mr. P.....	C. of Jaw.....	91	90	5,200,000	8,880	87.6	7.3	4.6	.3	0
54	Mr. P.....	Ep. of Cheek.....	190	90	3,904,000	11,700	84	10.5	4.5	1	0
59	Mrs. R....	C. of Breast.....	169	100	5,600,000	6,800	74	13.5	9.5	3	0
00	Mrs. R....	" " Skin.....	67	90	4,130,000	12,000	77.5	15	6.5	1	0
04	Miss R....	Chond-Sarc.....	206	100	4,928,000	10,000	57	13.5	28	1.5	0
99	Mrs. S....	C. of Breast.....	134	100	5,184,000	7,300	61.5	16	20	2.5	0
02	Mrs. S....	Ep. of Face.....	155	100	4,672,000	7,200	50.5	31	15.5	3	0
08	Mrs. F. S..	Sarc. of Phar.....	188	95	4,640,000	8,000	53	11	32.5	2.5	0
03	Mrs. S....	C. of Breast.....	102	100	4,928,000	7,000	61.5	22.5	13	2.5	.5
07	Mrs. S....	" " "	86	60	2,326,000	10,500	40	19	39	1	1
03	Mr. S.....	" " Jaw.....	175	100	4,376,000	6,900	60	16.5	21	1.5	1
00	Mrs. S....	" " Thyroid.....	174	100	5,230,000	7,400	72	18	7	2.5	.5
06	Mr. Von E.	Sarc. of Leg.....	118	100	4,640,000	7,800	60.5	20	14.5	4.5	.5
03	Miss W....	C. of Breast.....	217	100	4,960,000	9,000	72	16	9	2.5	.5
08	Miss W....	" " "	180	100	5,650,000	9,200	64.5	18	17	.5	0
01	Mrs. W....	" " "	155	95	4,288,000	8,600	64.5	19.5	18.6	3.3	.3
09	Mr. M.....	" " Rectum	91	80	4,072,000	7,520	69.3	11.6	18.6	.3	0
01	Mrs. W....	" " Ovary.....	93	95	5,632,000	8,100	54	25	17.5	3.5	0
	Average.....		152	95.5	4,782,000	8,270	64.4	18.3	15.6	1.9	0.2

Comparison with the preceding table will show characteristic progress during this period fourth and fifth months (on the average) of Autolysin treatment.

Nothing more would have been necessary to make the two ounts identical as to their leucocyte percentage balance than to ake the 9.5 per cent. in excess of polymorphs in the second case nd transfer them to the large monocyte column. I am greatly isposed to believe that had the Autolysin treatment been able to ffect such a modification of blood count, there would have been modification in the production of the leucocytic enzymes that ight have turned the scale in the patient's favor. As it was, owever, the second patient developed a small metastasis in the eck while undergoing the treatment, which so alarmed her that

Digitized by Google

she discontinued Autolysin, and went to another city for X-ray treatment. A few months later her death was reported.

What might have been the progress of the case had the Autolysin treatment been continued is of course only conjectural. But the blood count showed that the case was not progressing under the proteals as satisfactorily as could be desired; whereas the blood count of the other patient gave every warrant for the favorable prognosis that was presently justified.

Incidentally we might note that both these cases were cancers of the breast.

In another connection, I have suggested that when a patient under the Autolysin treatment has been carried to a stage of very marked improvement, progress may be retarded by excessive doses, putting a tax upon the corpuscles that is not compensated by further stimulus to the blood-forming organs. Obviously, the guide as to this must be found in the blood count.

In general, I would suggest that when the red-cell count has been brought to approximately five million, and the differential leucocyte count to the status above suggested, in which there is marked lymphocytosis with distinct preponderance of the large mononuclears, the physician should be chary of giving large doses of Autolysin.

It may be desirable to discontinue treatment altogether for a time; but it is usually preferable to restrict the size of dosage, and extend the intervals between doses. A dose of 10 or 15 minims given weekly or semi-weekly may keep the corpuscular response at a maximum, and foster progress that would be impossible under larger or more frequent doses. Yet the same case may have required dosage of 40 or 50 minims daily or on alternate days at an earlier stage.

All therapeutic rules have exceptions, however; so I must add that it appears sometimes to be advantageous to give a patient who has reached the static period the shock of a large dose, or of an intravenous injection, which produces a vigorous reaction. A case was recently reported in which, quite by accident, part of a dose was given into a vein. There was anaphylactic reaction within a few minutes, and subsequently the neoplasm began rapidly to regress, although it had for some weeks been static, after having passed through an earlier stage of favorable progress.

All this, however, only emphasizes the point made in an earlier section, to the effect that any one who can administer a hypodermic injection may begin the proteal treatment of a case of cancer, and for a time secure gratifying results; but that, even in cases that have larger possibilities, these possibilities can be realized only when the subsequent administration of the remedy is carried forward along scientific lines. One object of the present

Digitized by Google

section has been to suggest that the scientific administration in question necessarily connotes repeated observation of the blood count as modified by the administration of the proteal antigens.

SECTION IX.

CANCER AND THE LYMPHOID SYSTEM

There is one profoundly important aspect of the problem of treating cancer with proteins to which incidental reference has been made in this monograph, but which, so far as I am aware, has never been elsewhere suggested.

The point in question is this: Every cancer patient has been subjected to a spontaneous course of protein treatment before he comes into the hands of the surgeon or physician.

Such, at least, must be considered the fact if the thesis as to the nature of cancer that furnishes the basis of this monograph is accepted. According to that thesis, as elsewhere elaborated, there is incessant warfare from the outset between the blood corpuscles and the neoplastic cells, with the consequent destruction of combatants on both sides.

If the corpuscles win, the lawless cells are entirely eliminated, and no tangible neoplasm will result.

But if the new cells win, they ultimately constitute an aggregate that we call a tangible cancer. Meantime, there has been an effort on the part of the bodily defenders—namely, the white and red corpuscles—that has profoundly disturbed their status as health-defending agents. And needless to say this profound disturbance has extended to the organs that produce the blood corpuscles,—namely the bone marrow, the lymphatic system, and the spleen. Abundant proof of this is found in the presence of myelocytes, normoblasts, and abnormal lymphoid corpuscles in the blood stream.

The manner of change that brings about this modification of the blood conditions may be illustrated by a quotation from Dr. Ward's book on *Bedside Hæmatology*. In the chapter on "Generalized Affections of Blood-forming Tissues"—in which there is no specific reference to cancer—he says:

"It is well known that the most powerful and efficient stimulants of blood regeneration are the products of blood destruction. This is well shown in the case of Addisonian [pernicious] anæmia and in the results of injections of very small quantities of blood in cases of anæmia. We need not then be surprised if after this destruction we find excessive formation. We do, as a matter of fact, find both excessive formation of white cells and the pres-

Digitized by Google

ence of the products of excessive destruction in the urine. The next step in the pathology will be the reversion of the cell-forming organs to a more primitive type as a result of the continued strain on them. This also we find in lymphæmia as we do in Addisonian anæmia. Here, however, the analogy ends for the reversion in the case of lymphæmia may proceed in the extent of resurrecting tissues whose cell-forming days were over."

Elsewhere in the same chapter, the salient aspect of the subject is elaborated as follows:

"In the group of diseases now to be discussed the common and distinctive feature is involvement of all the blood-forming organs by a growth or overgrowth that is similar in each organ.

"In the first sub-group, the leukæmias, not only the adult blood-forming organs, marrow, spleen, and lymph glands are effected but in other situations tumors may appear which are composed of tissue identical with that in the marrow, etc. These tissues are the embryonic and infantile blood-forming organs, the liver and thymus, and, secondly, connective tissue wherever met with. This extraordinarily wide distribution of lesions in some cases is the more readily explained when we remember that all mesoblastic tissue is potentially blood-forming—*i.e.*, blood-cell-forming—just as it is potentially sarcomatous or fibromatous."

To understand the subsequent sequence of events, we have to recall that overstimulation of any organ leads presently to exhaustion. So the same stimulus that at first produces an excess of blood corpuscles may presently result in marked decrease. Note, for example, what Pappenheim says as to this:

"Leucopenia is not diametrically opposed to hyperleucocytosis even when it appears from the first as a leucopenia, e.g., in typhoid. It ought rather to be regarded as differing in degree only, since high degrees of leucocytosis, or leucocytosis of long standing, may merge into leucopenia. When this occurs, especially if accompanied by the presence of early forms [leucoblasts, myelocytes, normoblasts] in the blood, it indicates commencing exhaustion of the overtaxed bone marrow."

Such are the recognized effects of a persistent stimulation of the organs of blood regeneration by the products of blood destruction. It must be obvious, then, that in every far-advanced case of cancer, or at any rate in every case in which a neoplasm has assumed considerable proportions, there must be a greater or less degree of what Ward refers to as "hyperprophy of the lymphocyte-forming tissues," including spleen and marrow. According to the present thesis, the increased formation of lymphocytes and early myelogenous forms in response to the stimulus of the cancer cells is a salutary process,—an attempt on the part of the organism at spontaneous cure of the malady. But the net result, when the new growth is too active, is that ultimately the organs of blood-formation have reached their maximum response

Digitized by Google

to that particular antigen, and through prolonged overstimulation a general myelogenous and lymphatic maladjustment is produced which is in many respects comparable to the general leukæmias of different origin. "Many people," says Ward, "consider that leukæmia is of the nature of a malignant growth as, for instance, cancer of the stomach is a malignant growth." Again he says: "That there are analogies between cancer and the leukæmias no one will deny." He adds that in his opinion these analogies are not sufficient to bring the two into the same class; admitting at the same time that theories in the matter are at present only tentative, and going on to say that: "If leukæmias are cancer, then the metastases of cancer are not due to emboli from a primary growth nor to spread by direct continuity along lymphatics, but are primarily formed in each situation in which they occur under the influence of the same stimulus that produced the original tumor." To be sure, Ward thinks that most pathologists will not subscribe to this view of cancer metastases, and so will reject the analogy which suggests that leukæmia is to be regarded as a form of new growth of the bone marrow or glands. He adds, however, that "the theory and the analogy form a fascinating and possibly productive field for discussion and research."

There is no occasion here to enter into detailed discussion of the pathological questions involved. My object in referring to it is to emphasize the view that the presence of a cancerous growth implies a profound dyscrasia of the lymphoid tissues. There is of course nothing new in this view, although it may perhaps be said that there is novelty in the explanation of the fact just offered,—the suggestion, namely, that the lymphatic hypertrophy may be a direct result of the response to the antigenic stimulus of the decompounding cancer cells.

From a practical standpoint, the importance of the matter lies in the fact that a full recognition of the conditions will prevent anyone from supposing that he has effectively treated a case of cancer when he has merely removed a local neoplasm.

More specifically, the matter is important in the present connection as emphasizing the view that a cancer patient, before he comes into the hands of the physician, has undergone a radical course of protein treatment. This fact is immensely significant in its bearing on the practicalities of a subsequent course of protein treatment at the hands of the physician.

If the view just presented is accepted, for example, it becomes obvious that any further treatment based on the administration of cancer proteins (and such treatment has been suggested and extensively tested) would be illogical in the highest degree. All that cancer proteins can accomplish as antigens has already been accomplished, and the net result is that the patient still has a

Digitized by Google

neoplasm associated with a responsive dyscrasia of the blood-forming organs. Hence the futility of the autolysate treatment of Fichera and allied attempts to treat cancee with so-called" "vaccines" made from the tissue of neoplasms.

A disturbance of the blood count, or a deviation from the normal, in token of cytogenic dyscrasia, may be expected as a matter of course. If the neoplasm is small, as in case of a epithelioma of the mouth, the antigenic stimulus of the cancer cells may be of so relatively slight a character that the blood picture, at the time when the patient comes under observation, may be identical with that which has been presented in an earlier chapter as typically favorable. The red blood count may be above five million; the white count about 8,000; and the mononuclears may constitute 35 or 40 per cent of the leucocytes with a preponderance of large monocytes; and there may be relatively high percentage of eosinophiles.

This would indicate, according to the present thesis, that the patient in question is receiving spontaneous protein treatment that is accomplishing valuable results in retarding the progress of the malady.

More commonly, however, as records of our counts have shown, the patient at the time of first examination has reached a stage at which the corpuscular balance is much less favorable. The stimulus to the cytogenic apparatus (in particular the bone marrow), followed by exhaustion, is revealed in a relative monocypenia, but with marked preponderance of the small lymphocytes, associated with a deficiency of eosinophiles, and, usually, with a marked decrease of the red corpuscles. Commonly there is marked general leucocytosis, but with preponderance of the polynuclears. Myelocytes, leucoblasts, and normoblasts may be present in greater or less profusion. The polynuclears commonly shows marked deviations from the normal as regards the conformation of the nucleus (S-shaped nucleus, ring-form, spiral contortion, etc.), with in general a marked tendency toward "progression to the left,"—speaking in terms of the Arneth formula.

This pciture suggests that a spontaneous cancer-antigen treatment has passed its maximum of efficiency, and that relatively rapid and unfavorable progress of the neoplasm must now be expected unless a new and different stimulus can be brought to bear on the defensive mechanism of the body.

Such a new stimulus may be supplied by the X-ray, by radium, or by the administration of proteins of a type quite different from the proteins of cancer.

In discussing the action of X-ray and radium elsewhere I have suggested that the beneficial effect of these rays may be in part at least due to their general influence on the blood count. I wish

Digitized by Google

now to emphasize this aspect of the matter in the light of the statement above quoted from Ward to the effect that: "It is well known that the most powerful and efficient stimulants of blood regeneration are the products of blood destruction."

I am inclined to think that a large measure of the benefits sometimes unquestionably attained in cancer from the use of X-ray and radium may be explained as due to their destructive influence on the blood corpuscles. It is well known that in general leukæmias, the number of white corpuscles may be reduced by X-ray treatment. It is also known that radium exercises a destructive influence on the blood corpuscles. It follows that these influences must stimulate the blood-forming mechanism, inasmuch as their use tends to saturate the blood, more or less, with "the products of blood destruction."

In point of fact, we have observed that patients that had undergone X-ray or radium treatment before applying for Autolysin treatment sometime show a blood picture precisely of the kind that we have come to regard as favorable, and as indicating the best possible response to the proteal treatment itself. I am strongly inclined to the opinion that in many cases this favorable blood picture is directly due to the use of X-ray or radium, and that the beneficial effects of these treatments are in a large measure due to this general modification of the blood quite as much as to any local effect on the neoplasm.

Indeed I think it is an open question whether it may not be possible to get the good effects of X-ray or radium by treatment applied generally, or to the bones or to the spleen, rather than by prolonged application to the site of the neoplasm itself. This, however, is a matter that need not be discussed in detail in the present connection. It suffices to emphasize the opinion that prolonged exposure to X-ray or radium at the site of the neoplasm is inadvisable; and that the danger of local burns, with their characteristically disagreeable and resistent ulcers, may be obviated without sacrificing any of the expected benefits, by shifting the locus of treatment.

Incidentally, it may be noted as a matter of interest that radium, when introduced into the animal organism, is believed to have something like an elective affinity for the bone marrow, taking permanent lodgment there. So, at least, I have been informed by one of the most experienced workers in this field, who stated this as a matter of fact, quite without reference to any theory as to the action of radium on the blood-forming mechanism.

It is the commonly accepted opinion of pathologists that, whereas the X-ray exerts a temporarily beneficial effect in the treatment of leukæmias, the effects cease to be cumulative after a time, and ultimately the beneficial response ceases, and the patient goes

Digitized by Google

on to a period of decline, which the X-ray now seems powerless to retard.

We must expect, I think, that the same thing will ordinarily be true of the X-ray or radium treatment of the type of lymphæmia or myelæmia associated with the presence of malignant neoplasms. It was above suggested that the neoplasm assumes significant proportions only when the blood-forming mechanism has ceased to respond effectively to the antigenic stimulus of the cancer proteins. When this has occurred, a new stimulus may be given to the blood-forming apparatus by X-ray or radium treatment. In a certain number of cases, this new stimulus may be sufficient to turn the scale in favor of the bodily defenders, and against the neoplasm; with the result that the lawless cells are totally disintegrated, and a condition of at least clinical cure is effected. But in a much larger proportion of cases, it cannot be hoped that the new stimulus given by the radiation treatment will serve to turn the tide so effectively. In a vast preponderance of cases, the neoplasm will be found to be so thoroughly fortified that it offers successful resistence to the best fighting equipment that the body can develop under the new stimulus.

Even where the local neoplasm seems completely to disappear under the new stimulus, it is a matter of unfortunate observation that either direct or metastatic recurrences presently reveal themselves, showing that the profound lymphatic dyscrasia, however modified, has not been eliminated.

In such a case (and this is equivalent to saying, in practically all cases of cancer), it is desirable to seek still other methods of stimulating the cytogenic apparatus, and thus further to fortify the fighting equipment of the body. The therapeutic agents available for this purpose include: (1) Hygienic measures, such as proper food, exercise, massage, and cold baths; and (2) An indefinite series of foreign proteins, animal, bacterial, and vegetable.

The discussions of the present section must have made it clear that present experience gives no theoretical warrant for the assumption that any one of the foreign proteins in question can be expected to whip up the blood-forming organs sufficiently to enable the body to eliminate the neoplasm when it has reached an advanced stage, and restore normal conditions. But fortunately a long series of proteins is available, and it would appear that each one of them is capable of bringing a stimulus of a new type, and thus of taking up the work to some extent where the preceeding proteins left it.

The antigenic influence of the cancer cells themselves did something in the beginning to stimulate the defensive mechanism, but their beneficent influence came presently to a standstill, while their malignant influence continued.

Digitized by Google

The X-ray and radium added an increment of new stimulus, in effect bringing new legions of corpusclar warriors into the field; but in the end they also failed, though their work was by no means insignificant.

Now a new protein antigen may be administered hypodermically by the physician, with the result of bringing further recruits from the cytogenic outposts.

And when this stimulant also has reached its maximum, the physician may turn to a second protein and yet a third, or to new combinations of proteins; in the hope that ultimately the corpuscular legions thus invoked may effectively disintegrate the last cancer cell.

It is the main purpose of the present monograph to suggest that non-toxic vegetable proteins may have a large share in this work; but I would by no means affirm that they are necessarily the only available proteins. If the general principle that what we are seeking is a protein antigen that will produce a corpuscular response of a pretty definite kind is fully grasped, the physician selecting the treatment may experiment for himself with different proteins, finding doubtless that some patients respond better to one and others to another. At first the fight will be a hard one, but it does not seem a hopeless one so long as an endless series of proteins is available and the organism appears capable of taking on new responsive activities with the introduction of each new protein.

At the time when this monograph is issued (December 1, 1916), we are testing at the Beebe-Williams Clinic a considerable variety of proteins that have not hitherto been used in a similar way as therapeutic agents. These include, in addition to various combinations of the twelve products making up the original proteal mixture, the proteins of alfalfa seed, of hemp seed, and rape seed, as already mentioned; proteins extracted from alfalfa meal, made by grinding up of the entire plant; and the proteins of various food products, including egg albumin, milk albumin, wheat albumin, and sundry other food products. It is our intention ultimately to test the entire list of proteins that enter into food products. Incidentally, I may mention that as the proof of this section is passing through my hands, a report from a California physician tells of a case of asthma treated with egg albumin with gratifying results in response to my recently published general exposition of the thesis of non-specific protein therapy.

Mention has already been made of the different response to the same dosage of different proteins. It has been suggested, also, that the relative response is conditioned on the frequency with which the organism has come in contact with a given protein in

Digitized by Google

the past. It is consistent with this assumption to note that the protein of alfalfa seed gives a more severe general reaction than a corresponding quantity of the proteins of hemp seed and rape seed, and of the various food products hitherto tested. We are not yet in a position to express a positive opinion as to whether a severe general reaction is ever to be desired in the treatment of malignant neoplasms. It should be observed, however, that some of the best results have been attained in cases in which there was severe reaction. A case of very marked improvement under the use of alfalfa protein, after the earlier combination of vegetable proteins apparently lost its responsive capacity, has already been cited.

In general, however, we do not in practice attempt to secure a severe reaction. On the contrary, we prefer that the patient should experience no untoward effects from the medication from day to day, and we attempt to regulate the dosage in such a way that there shall be no severe reaction. Very commonly there is no reaction whatever, local or general, of which the patient is cognizant, although the improvement in general condition may be conspicuous.

It may not be amiss to state that the genralizations just made are based on the records of about four hundred cases of cancer, including carcinomas, epitheliomas, and sarcomas located in almost every region of the body, treated with proteins at the Beebe-Williams Clinic; fortified by the records of several hundred additional cases treated by physicians acting independently in various parts of the country. As bearing on the authenticity of the latter records, it may be stated that more than four hundred physicians who have used Autolysin in the treatment of cases of inoperable cancer are members of the American Medical Association.

SECTION X

ANIMAL EXPERIMENTATION AND PROTEAL THERAPY

About the year 1908 Dr. Silas P. Beebe and Dr. George W. Crile, were experimenting with transplantable tumors in dogs. They found that with dogs, as with rats and mice, some individuals seemed immune to the transplantation of such tumors. In other cases, the tumor after transplantation grows for a time and then "spontaneously" regresses. In yet others, it continues to grow until it brings about the death of the animal. As with

Digitized by Google

rats and mice, the dog that had recovered through "spontaneous" regression of a tumor appeared to be immune to subsequent transplantation.

It occurred to the experimenters to test the effect of transfusing the blood of such an immunized animal into the vascular system of a dog in which the transplanted tumor was progressing. Experiments were first made with the blood serum of the immunized dog; and the results were negative. But when, subsequently, transfusion was made of the whole blood of the dog, a curative result was observed, the tumor in the affected animal regressing, and the dog going on to complete recovery.

It seemed fairly obvious, then, that there was something in the entire blood of the animal that was not conveyed with the serum alone that served as an antagonist to the cancer cell. Dr. Beebe recalls that on one occasion a not unnatural suggestion was made by a visiting physician who had witnessed the results of these experiments to the effect that possibly this curative principle might reside in the bodies of the leucocytes. The suggestion was recognized as having interest and plausibility, but the trend of thought at the moment was in the direction of chemical explanations of a less tangible kind, and no immediate attempt was made to verify or refute the leucocytic hypothesis. The matter came naturally to mind, however, when several years later, observation was made of the modification of blood count under influence of the protein treatment of human cancer subjects.

When the series of blood counts made in the Beebe-Williams Laboratory had reached the stage at which it became evident that there were highly interesting modifications of the leucocyte count (specifically characterized by an increase of mononuclear leucocytes, and in particular of the large mononuclears), it became a matter of interest to examine the literature of experimentation in quest of records of analogous experiences.

Then it became apparent that there is a peculiar paucity of observations on the differential count of the white corpuscles in an otherwise expansive literature; due, no doubt, to the fact that most workers have been concerned with the biochemical rather than the histological aspects of the investigation. It was, I think, the late Elbert Hubbard—voicing a familiar conclusion—who made the cogent observation that, in matters of science, we appear always to progress from the complex to the simple, and that the obvious is the last thing to be observed. Experiments in cancer inoculation with animals would seem to furnish another illustration of the truth of this observation, inasmuch as very tangible and obvious modifications of the blood count have for the most part been overlooked by workers who were concerning themselves with intricate problems of bodily metabolism involv-

Digitized by Google

ing chemical conditions susceptible of investigation only by the most delicate of biological methods.

Fortunately, however, there are a few workers who appear to have been impressed with the histological aspects of the problem, although even these have for the most part considered this aspect of the subject as having only subordinate interest.

Among the earliest and most important observations that associate the leucocytes with the process of immunization of animals against cancer inoculation are those of Bashford, Murray and Cramer, working under the auspices of the Imperial Cancer Research Fund, in England. In a report published in the Proceedings of the Royal Society of London for 1909, dealing with the general subject of resistant cancer inoculation, in mice, they make the following highly interesting observations:

"The phagocytosis of formed cellular elements plays an important role in inducing resistance; serum is impotent to induce resistance, blood corpuscles do so. The energetic phagocytosis which accompanies the spontaneous absorption of transplanted tumors, and which occurs in absorption after exposure to radium, speaks strongly for the conclusion that the processes are the same in kind when blood or tumor cells, being absorbed, produce resistence. But we are as yet unable to determine the extent to which agencies directed against the tumor cells themselves may assist in determining their early death in protected animals."

At an earlier stage of the series of investigation, the role of the leucocyte had been under consideration, as shown by a report made by Bashford, Murray, and Bowen, in the Proceedings of the Royal Society for 1906. In this report the authors say:

"Of course the cells presenting complete degeneration are no longer capable of giving rise to tumors. In fact they are rapidly taken up by the phagocytes in the days immediately preceding transplantation, and it might be concluded that growth was continued by cells which never tended to degenerate."

Incidentally it is of interest to note that in connection with this report the authors show a drawing of inoculated tumor tissues undergoing degeneration, in which portions of the mass that stain lightly are surrounded by cells with dark-staining nucleus and protoplasm of a type closely similar to cells that we have observed at the Beebe-Williams Clinic in a patient's blood taken from the immediate sustance of a cancerous mass.

In continuance of the same line of observation, we find Da Fano in the Fifth Scientific Report of the Imperial Cancer Research Fund, issued in 1912, referring to the round cells that occur in the margin of a tumor that is retrograding, and along the strands of actively proliferating connective tissue. Da Fano suggests that the development of tumor immunity in mice is coincident with the general reaction of the connective tissue throughout the organism. He observed that the polynuclear leu-

Digitized by Google

ocytes appear first at the place of the implanted tumor, and ndergo degeneration, without showing phagocytic activity. The ymphocytes then appear in large numbers in the region of the noculated tumor, gradually diminishing after immunity is estab-ished. According to his observation, inoculation of dead tumor ells was not followed by round cell infiltration nor by the de-elopment of tumor immunity. The observations were thought o establish a close relationship between the leucocytosis and the levelopment of tumor immunity.

Dr. F. W. Baeslack, of Detroit, Mich., was led to take up a pecific investigation of the modifications of the leucocytic blood ount in mice suffering from transplanted tumors. The results of is researches were published in the *Zeitschrift für Immunitats-orschung* for 1913. He points out that the observation of the ncrease of leucocytes in cancer was made as long ago as 1843 y Andrae, and confirmed in detail by Lüdke in 1867. The latter bserver concluded "that the increase in the number of leucocytes vas a sign that the disease had become general and involved the vhole body." Reference is made to other workers who have nade observations on the leucocytes in cancer, but the list is a urprisingly short one considering the enormous bulk of cancer iterature in general.

Dr. Baeslack's experiments had to do with several series of noculated cancer mice. He states that his count of the blood ells included the large mononuclears and the eosinophiles, but is percentages and charts are given only for polynuclears and mall lymphocytes. As to these he says:

"It is of interest to note that the small mononuclear lympho-ytes decreased during the period of active tumor growth, while he polymorphonuclear leucocytes increased, and that shortly be-ore the retrogression of the tumor became noticeable the rela-ionship between these two classes of cells was entirely changed."

The charts presented give graphic illustration of the observa-ion that when the polynuclear leucocytes went up and the small ymphocytes went down, the case was progressing badly. In ne case at an early stage the polynuclears went up to 55 per ent. and the lymphocytes went down to 26 per cent. (It must e recalled that the polynuclears are relatively sparse—16.9 per ent., according to Price Jones—and lymphocytes relatively bundant—59.7 per cent.—in normal mouse-blood). But at a ater stage, when the tumor was undergoing regression, the olynuclears went down to 16 per cent. (substantially normal), nd the small lymphocytes advanced to 48 per cent. of the total eucocyte count, a number probably within the limits of normal ariation.

Digitized by Google

It is unfortunate that details are not given as to the remaining types of leucocytes, but it is obvious that a simple computation shows that at the earlier stage of this experiment, when the tumor was seemingly overmastering the system, the large mononuclears and the eosinophiles together aggregated only 19 per cent. of the leucocyte count; whereas at a later stage, when the tumor was spontaneously regressing, the large monocytes and the eosinophiles together must have aggregated 36 per cent. of the total count, a number far in excess of the normal, which, according to Price Jones, is represented by 21.5 per cent. of large mononuclears and 0.14 of eosinophiles.

These observations of general lymphocytosis in cases of mouse tumors that are progressing to recovery have obvious interest as supplementing the observations of Da Fano to the effect that lymphocytes appeared in great numbers about inoculations of immunizing material during the evolution of resistance, and that in growing carcinomata the presence of the lymphocytes in great numbers was clearly associated with a local healing.

Further association between the corpuscles and the processes of immunization was suggested by the observations of Lambert and Haynes that rat sarcoma would grow in the plasma of immunized mice quite as vigorously as in that from normal or tumor-bearing animals,—an observation that obviously links with Beebe's observations on the curative properties of entire blood versus serum, as recorded at the beginning of this chapter.

From the present standpoint these observations as a whole have quite exceptional interest because they reveal modifications of the leucocyte count in mice in which tumors are undergoing regression that are singularly comparable to the records of the favorable cases of human cancer under protein treatment at the Beebe-Williams Clinic, as recorded before the observer had so much as heard of Dr. Baeslack's experiments. It will be recalled that charts were presented to illustrate graphically the fact that in cases that progressed most favorably under proteal treatment the polynuclears and the small lymphocytes tended to approach the normal in numbers, whereas the large monocytes increased very markedly and held at high level.

It would appear that the same formula could be applied to Dr. Baeslack's convalescing mice; although the observer himself obviously failed to appreciate the significance of the large monocyte count, his attention being fixed solely on the polynuclears and small lymphocytes. Possibly he had overlooked, or was not aware of, the normal balance of leucocytes in mice (which, as just noted, is very different from that of the human subject), and hence did not realize that the fall of polynuclears to about 16 per cent. and the rise of lymphocytes to about 50 per cent., represented only

Digitized by Google

approximations to the normal; whereas the really significant feature of this count had to do with the large monocytes, which rose far above normal as the case progressed favorably (as we learn by subtracting the polymorphs and lymphocytes from the total count), yet which he did not think it worth while specifically to enumerate.

This correspondence between clinical experience with the human subject and laboratory observation of mice, as regards the modifications of leucocyte differential count when the system appears to be getting the better of a cancer invasion, is at least highly suggestive.

That Price Jones should have noted a rise of large monocytes in cancerous mice presumably not progressing favorably is obviously consistent with the thesis concerning the response to the presence of cancer cells exposited in detail in an earlier chapter of the present work; and it may be observed that the mice in question, as studied by Price Jones, showed increase in polynuclears also, precisely as did Baeslack's mice that were not recovering.

Of course it will not be overlooked that rise of polynuclears, taken by itself, is a phenomenon familiarly associated with bacterial infections, and that the latter may occur as a complication in many cases of malignant involvement. But it will be obvious that the modification of the differential count recorded in the Beebe-Williams charts is altogether different from that induced by bacterial infection, inasmuch as a characteristic feature is the reduction rather than the increase of both relative and absolute polynuclear numbers.

Meantime it should be observed that students of the infections have tended to focus attention on the polynuclear "microphages" to the neglect of the mononuclear "macrophages." Even where the latter were counted, the possible significance of modifications of their numbers, is frequently overlooked or ignored. Thus in the very interesting and important studies of Gay and Claypole, as recorded in the *Archives of Internal Medicine* for November, 1914, in which the leucocytosis induced in normal and immunized rabbits by the injection of *Bacillus typhosus* is studied differentially, stress is laid entirely on the increase in polynuclears, although the facts recorded permit interesting inferences regarding the large mononuclears also, since the actual count of these cells twenty-four hours after inoculation showed an increase per cubic millimeter from 670 to 3,014—a four-and-a-half-fold advance. It is true that the advance of polynuclears was even more overwhelming (from 5,226 to 60,480); but on the other hand, the small lymphocytes advanced only from 7,370 to 11,340, an increase of but 54 per cent. suggesting by contrast that the four-and-a-half fold advance of the large lymphocytes is not to be

Digitized by Google

explained as a mere incidental result of general excitation of the blood-forming mechanism.

It is noteworthy in this connection that German clinicians (for example Von Domarus) cite an increase of large mononuclears as a typical feature of the secondary stage of a so-called "leucocyte-curve" of infections, such increase following the primary advance and recedence of the polynuclears, and preceding the advance of the small lymphocytes. Conceivably this macrocytosis is to provide for the hydrolysis of the protein products with which the blood has been flooded by the disintegration of the microphages (polynuclears) with their increment of partially digested bacteria. Such at any rate, might be a plausible explanation of the later aspects of the "leucocyte curve" if the polymorphic thesis as to the proteolytic activities of large and small lymphocytes is accepted.

In general, it would appear that a relative macrocytosis betokens a non-bacterial protein invasion as clearly as a neutrophile increase betokens a bacterial infection. Probably the diagnostic value of the macrocytosis is not less than that of the polyneuclosis, although hiterto quite unrecognized.

Further pursuance of the subject here, however, would carry us too far afield from the present theme, which concerns malignant neoplasms rather than general infections. Let us again take up the analysis of the results of animal experimentation in the cancer field, with an eye to the correlation of these results with our own clinical and laboratory experience with cancer in the human subject.

Cart Before Horse

In considering various of the observations above cited, and numerous others in the literature of transplantable tumors in rats and mice, one is led to reflect on the power of preconception and the difference that may result from a changed point of view.

If a person who had seen automobiles moving about the streets, but who now for the first time saw a horse and carriage, were to describe what he had seen, he would doubtless tell of an automobile that pushed before it a strange animal. He might even note with amusement that the animal was obliged to move very rapidly to keep ahead of the vehicle that tends to overrun it. Probably he would be led to query why it would not be more convenient to tie the animal behind the vehicle and thus avoid the danger of injuring it.

Now such a description of the locomotion of the horse-drawn vehicle would, in my opinion, be strictly comparable to the descriptions that have appeared in the literature of cancer in connection with the question of the transplantation of tumors and the giving

Digitized by Google

of immunization. As a case in point, note the comment of a very industrious and laborious compiler, reviewing the literature of the subject, when referring to the experiments of De Fano, above noted, as follows:

"As lymphocytes appeared in great numbers about inoculations of immunizing material during the evolution of resistance, their relation to this condition could not be denied. . . . In growing carcinomata they were to be found only in places where local healing was in progress. A carcinoma cell seemed to exert some sort of specific influence on the lymphocyte, and the latter to spread the resistant state throughout the organism."

In the light of the interpretation of the action of the lymphocytes that furnishes the chief thesis of the present monograph, which will be elaborated presently, such a phrasing seems not less ridiculous than the suggestion that the horse is pushed before the carriage.

To say that lymphocytes "were found only in places where local healing was in progress" is a little as if one were to note the curious coincidence that, in a certain house, rats were to be found only in places where cheese was disappearing.

Scarcely less absurd seems the interpretation that has been put upon the widely heralded experiments of Ehrlich, as repeated by others, in what has come to be known as the zigzag transplantation of tumors. It will be recalled that in this experiment a tumor from a mouse is transplanted to the body of a rat, where it grows for a time, and then begins to undergo regression. Before it has entirely regressed, it is taken from the body of the rat and transferred to the original host, where it again takes on more or less energetic growth. It will be recalled that Ehrlich explained this with an elaborate theory of so-called atrepsia, according to which there are certain chemical constituents in the organism of the mouse that are essential to the growth of the mouse tumor; that a certain quantity of this material is transferred with the tumor to the body of the rat, and that when this transferred portion is exhausted, the growth can no longer continue in the body of the rat.

In the light of the present thesis, the explanation of zigzag transplantation would be simply that the transplanted tumor grew for a short time in the body of the rat because a certain time was required to muster the companies of corpuscles to combat the lawless cells. When the corpuscular defenders had been aggregated in sufficient numbers, the fight with the cancer cells would turn in favor of the host, and the cancer would begin to regress. Now, however, the remainder of the cancer cells are retransferred to the mouse, where, as a matter of course, they continue to grow because it had already been demonstrated that the body of that particular mouse was not competent to produce corpuscles and their

Digitized by Google

enzymes in sufficient quantity to combat the activities of the cancer cells.

A similar explanation, obviously, may be found for the observed fact that an animal may be rendered immune to inoculation experiments not merely by inoculation with the cancer tissue, but with tissues of various kinds, including heteromorphous ones. For example, Dr. Isaac Levin reported the immunization of rats by treatment with mouse tissue. (Proceedings of the Society for Experimental Biology and Medicine, 1910.) Other experimenters have produced immunization with the tissues of liver, spleen, and other organs. The evidence seems to justify the expectation that immunity may be developed by the introduction of various protein substance, whether derived from the tissues of animals of the same species, or of other species. In a word, it would appear that we have to do with a general protein reaction. Couple these observations with the observations of Bashford and his associates and of Baeslack, and we might fairly expect—were not our minds turned in the opposite direction—that an essential modification of the leucocyte count would be found in all of these cases; and we might justify the inference that such modification had an important relation to the process of immunization.

When, now, we turn to the human subject, and study the modifications of the blood count in cancer cases, and in particular cancer cases under protein treatment, as reported in the present monograph, it is obvious how all these observations of the animal experimenters harmonize with the results shown in our charts; and the conclusion seems inescapable that we have to do with a general principle of protein reaction, and with a response of the blood-forming organs one prominent feature of which is an increase in the phagocytic or enzymic activities of the corpuscles. This, after all, is only giving specific application, in terms of the proteomorphic theory, to the general conclusion stated by Levin in the paper above cited on the immunization of rats with mouse tissue, to the effect that: "The explanation must be sought in some protective substance within the host created under the influence of the implanted mouse tissue."

Phagocytic Activities

Before going on to a more detailed exposition of what I conceive to be the character and manner of action of this "protective substance," I would introduce a quotation from Starling's standard work on Physiology to remind the reader of the really extraordinary part that phagocytic activities play in physiological processes.

"We have seen," says Starling, "that the leucocytes from whatever animal they may be taken present two phenomena, viz., that of

Digitized by Google

amoeboid movement and that of ingesting foreign particles which may be presented to them. On account of this power of eating up foreign particles they are frequently spoken of as 'phagocytes,' in this respect resembling unicellular organisms and the undifferentiated cells of many kinds of tissue. All the phenomena connected with the process of *inflammation* in higher animals are directed to the assemblage of leucocytes at the spot which is the seat of injury or of infection, so that they may devour and remove either the injured tissue or the invading micro-organisms. This process plays therefore an important part in determining the immunity of any animal against infection; though in the higher animals it is assisted by a number of other mechanisms directed towards the same end, which we shall have to discuss in a subsequent chapter. The use of phagocytosis is not, however, confined to the protection of the organism against infection. Wherever any effete or dead tissue has to be cleared away, whether as the result of injury or in the course of metamorphosis of organs, the leucocytes play an important part. Thus in the great rearrangement of tissues which occurs in the larval state of insects, the removal of the muscle fibres which are no longer required is effected by the accumulation of phagocytes around them. The phagocytes may send processes into the muscle substance, which dissolve this tissue and then take it up. The absorption of the tail of the tadpole is effected in the same way by means of phagocytes. In mammals, including man, the moulding of the long bone which occurs in the process of growth is effected by continual and coincident processes of absorption and new formation of bone. The absorption is carried out by means of spinal phagocytes formed by the aggregation of a number of leucocytes, the well-known 'giant cells' or myeloplaxes which form so prominent a constituent of bone-marrow.

"The blood-corpuscles represent the *wandering* phagocytes of the body. There are *fixed* phagocytes of which the myeloplaxes just mentioned may be regarded as a type. Other members of this class are the endothelial cells (Kupfer's 'Sternzellen') which line the capillaries of the liver. If a suspension of carmine or of micro-organisms be injected into the blood stream these endothelial cells are found a little later to have taken up large numbers of the foreign bodies. Under normal circumstances these cells as well as some similar cells in the spleen take up effete red blood-corpuscles and destroy them. During the process of degeneration of a peripheral nerve brought about by its separation from the ganglion-cells of which its fibres are the processes, a marked proliferation of the nerve-nuclei takes place. These become surrounded with protoplasm and act the part of phagocytes, loading themselves with the fat globules set free by the degeneration of the myelin sheath. To the same class of fixed phagocytes may possibly be ascribed certain of the plasma-cells of the connective tissues.

"That the polymorphonuclear leucocytes are endowed with these phagocytic properties is universally acknowledged, but some

Digitized by Google

doubt still exists as to how far the other types of leucocytes which we have described can function as phagocytes. It is probable that the lymphocytes, and certainly the large mononuclear or hyaline corpuscles, are endowed with these properties. The granular corpuscles, namely, eosinophile and basophile, are thought by some to function as unicellular glands and to react to infection, not by englobing the micro-organisms, but by discharging substances stored up in their granules which have a poisonous effect on the micro-organisms, and so prepare them for subsequent ingestion by the polymorphonuclear leucocytes."

A very striking illustration of the phagocytic activities of leucocytes is given in certain abnormal conditions, notably in so-called phagocytic anaemia. This condition is characterized by active phagocytosis of blood cells by other blood cells of normal or abnormal type in the circulating blood. Ward says of this: "The resulting blood picture is very striking. In one case the phagocytosis was so pronounced that it was calculated that if all the cells were as actively phagocytic as one which was observed actually in perfect cells on the warm stage, the whole of the red cells of the body would have been destroyed in less than two hours. In this case the destruction produced a fatal anaemia. Other cases have followed transfusion or have been associated with some known haemolytic process such as cholaemia. Isolated phagocytic cells may be met with in malaria and leukaemia and no doubt in other diseases."

The active share that the large mononuclear leucocyte takes in this process is noted by Ward and graphically depicted in a drawing showing large mononuclear phagocytes, "Many of them containing several cells or portions of cells which have been caught." One of these mononuclear phagocytes appears to have engulfed no fewer than seven red corpuscles. Another has engulfed two large cells that have the appearance of polynuclears. The picture gives graphic support to the nomenclature of Metchnikoff, who designated the polynuclears as microphages and the large mononuclears as macrophages.

These activities of phagocytes may be recalled in connection with the observations already cited of similar functioning in the removal of the detritus of cancer cells, as noted by Bashford and his associates. It may be noted also that Walker, in dealing with the effect of certain serums on carcinoma in mice, observes that if pieces of tumor are placed in the serum of a rat which has been injected with extract of mouse testis, degeneration of the cancer cell takes place, the cells being invaded and replaced by leucocytes. It does not appear that this observation has been verified by other workers, but it has obvious interest in connection with the not dissimilar observations of the other workers already cited. In particular, note the observation of Bashford, Murray, and

Digitized by Google

Cramer as to the "energetic phagocytosis which accompanies spontaneous absorption of transplanted tumors, and which occurs in absorption after exposure to radium," and the observation of two of the same workers that cancer cells presenting complete degeneration "are rapidly taken up by phagocytes in the days immediately succeeding transplantation."

All in all, it would appear that there is abundant warrant for the assumption that the leucocytes have an important share in the attempt of the organism to combat the invasion of cancer cells. Probably the evidence justifies the belief that they have *the* important share, though the co-operation of the red corpuscles is so essential (according to the present thesis) that these agents can scarcely be said to be subordinate.

If this conclusion is justified, it would seem to follow as a matter of course that a medicinal agent to combat cancer should be sought along the lines of a stimulus to the blood-forming organs. It does not appear, however, that any one definitely formulated such an idea until an agent clinically observed to benefit the cancer subject was found to have acted through stimulation of the blood count—in particular increasing the numbers of red corpuscles and large mononuclears.

Types of Leucocytes

It will have been observed that throughout the foregoing discussion we have been concerned with concrete and tangible facts. Let us supplement these facts by recalling the series of tables in which it was demonstrated that the administration of vegetable proteins brings about, in the average cancer case, a conspicuous and progressive increase of the large mononuclear leucocytes, which were seen to advance from the normal maximum of four or five per cent. of the leucocyte count to 15 per cent., 18 per cent., 19 per cent., and 25 per cent., on the average, in successive groups of cases; reaching a much higher figure in individual cases.

With these series of facts for background, it will not be without interest to make inquiry as to the manner of action through which the increased armies of large monocytes exercise their antagonistic influence against cancer cells, and thus benefit the patient.

At the outset I would suggest the advisability of not drawing too sharp a line of distinction between the two types of mononuclear leucocytes, namely, the small lymphocytes and large monocytes. It must be recalled that there are still differences of opinion as to the origin of the large monocytes, some physiologists contending that they are merely overgrown lymphocytes. A more popular view, probably, is that they are of bone-marrow origin,

Digitized by Google

and the progenitors of the polymorphonuclear leucocytes. But whichever view is correct, it is scarcely in question that the mononuclear leucocytes represent a somewhat more primitive type of cell than the polynuclear. The polymorphs, eosinophiles, and basophiles are of granular structure, and it is held that the granules have a secretory function, generating enzymes that escape into the blood plasma. In keeping with this function, these cells have in general a relatively large cytoplasm, and their nuclear structure, although elaborated and differentiated in form, is relatively sparse, particularly in case of the fully developed polymorph.

Meantime, the typical lymphocyte is almost exclusively composed of nuclear structure; and the typical large monocyte has a relatively enormous nucleus and a relatively small amount of cytoplasm, as contrasted with the typical polynuclear cell. There is, however, a type of large mononuclear with nucleus less basic in stain than the typical large monocyte, and with full clear cytoplasm, which my personal studies lead me to associate with the cancer-cell destroying process, and which I am disposed to regard as of lymphoid origin—in effect an overgrown lymphocyte. Fuller discussion of the status of this and other types of large mononuclears is reserved for a later chapter.

In substantiation of the idea that the mononuclears are of a somewhat more primitive type than the polynuclears, we find the former relatively abundant in lower animals—for instance, the rabbit, with 60 per cent. of mononuclears; and the mouse, as already cited, with 80 per cent. or more of mononuclear cells, one-fourth of them large monocytes, and 17 per cent. of polynuclears, contrasted with the 70 per cent. of the latter in the human subject.

Witness also the fact that children show a relatively high percentage of mononuclears, at once evidencing the primitive character of these cells, and suggesting that they in some way functionate in connection with the control of rapidly growing tissues. In the first and second years of childhood, according to Von Domarus, the polynuclears represent only about 42 per cent. of the total leucocyte count, the small lymphocyte representing 47 per cent., the large monocyte (including transitionals) about 8 per cent., and the eosinophiles about 3 per cent. By the fifteenth year, the polynuclears have risen to more than 56 per cent., and the lymphocytes have dropped to about 28 per cent., but the large monocytes and transitionals are slightly more abundant than in infancy, representing about 9 per cent. of the leucocyte count, while the eosinophiles have risen to not far from 6 per cent. Between puberty and adult life there are further changes, resulting ultimately in giving the polynuclears a census not far from three-quarters of the total leucocyte count; the lymphocytes being

Digitized by Google

about one-third as numerous, and the large monocytes dropping to relative obscurity with a count of from two to four per cent.

It would appear, then, that the physiological conditions in the body of the normal mouse call for about five times as many large monocytes, proportionately, as are required in the body of an adult human being; and that the normal human being during childhood and adolescence requires about twice as many monocytes as are subsequently called for.

Note now the suggestive fact that, according to the observations of Cramer and Pringle, the tissue of a cancer (in mice) is of an embryonic type, as shown by the fact that its cells contain only about seventy per cent. of the nitrogen content of the average tissues of the host. Cramer had indicated the similarity between the growth of cancer and the growth of the foetus, and preliminary experiments by Dr. Lochstad had shown that a rapidly growing tissue (foetus) has a lower nitrogen value than the maternal organism. These experiments obviously confirm the old ideal that cancer tissue is of somewhat embryonic character, and suggest the possibility that chemical or other agents might be found that would serve to decompound the cancer cells without injuring the normal surrounding tissue.

Natural Immunity and Artificial Immunization

Consider now for a moment the attitude—if the word be permitted—of the normal organism toward intruding cancer cells. Here the evidence must come largely from the field of animal experimentation, but it offers suggestive hints that may be applied, with due reserve, to the human subject.

It is familiarly known that the pioneer work of Hameu and Morau, expanded a little later by the work of Jensen and Leo Loeb, made possible a new era of investigation by showing that carcinomas and sarcomas of white mice and rats could be transplanted into other animals of the same species. It is equally well known that all experimenters are agreed that a certain number of individual animals show resistance to such transplantation, tumors embedded in their tissues regressing and disappearing "spontaneously" instead of continuing their lawless growth.

Thus it is shown, as Dr. Isaac Levin has phrased it, that "the growth of the implanted tumor depends upon the correlation between the virulence of the implanted cell and the resisting power of the organism of the host."

It was further shown that an artificial tumor used for inoculation appears to acquire increasing virulence as it is passed from one animal to another. But, on the other hand, it is possible to induce a condition in the body of an animal which at first is sus-

Digitized by Google

ceptible that will render it immune to further transplantation. This was done by Ehrlich and his associates by making an original inoculation with a tumor known to possess a low degree of virulence. Such a tumor being absorbed "spontaneously," it was observed that the animal in which such spontaneous absorption had occurred was now immune against inoculation with tumors of a more virulent type which would almost certainly have grown had not the animal been given added powers of resistance by the original inoculation.

What is of peculiar importance from the present standpoint is the fact that it was shown presently that inoculation with normal tissue, such as liver, spleen, and blood produced a degree of immunity comparable to that produced by the inoculation with a mild type of cancer cell. And most interesting of all is the observation of Dr. Levin and others that identical results as to induced immunity may be brought about by inoculation with so-called autolyzed tissue, that is to say, with tissue "of which the cells are killed in such a manner as to leave the endo-cellular enzyme-like substance uninjured and active."

I have quoted Dr. Levin's own phrase as to the use of autolyzed tissues, chiefly because it probably expresses the general attitude of mind of experimenters toward this particular aspect of the subject, in that it inferentially ascribes the immunizing influence of the autolyzed tissues to their "enzyme-like substance." It is hardly necessary to tell the reader of the present monograph, however, that in my own opinion the success of the experiment was due not to the presence of any specific enzymes, but to the fact that the tissue used—cancer tissue, liver tissue, spleen, blood, or what not—had the all-important advantage of being protein-bearing tissue.

This conclusion, to be sure, is inferential; but I think it will be admitted to find strong support in the fact that all manner of tissues, including even the tissues of an animal of another species (mouse tissues introduced into the rat, for example), can produce seemingly the same condition of immunity.

Note, now, the very significant fact that when a dog was cured of a transplanted tumor by the transfusion of blood of an immune animal in Dr. Beebe's later experiment at the Loomis Laboratory, it was shown that decompounding and absorption of the tumor itself was an essential part of the immunizing process. This was proved by the fact that it was not found possible to render a dog immune to transplantation of a tumor by transfusing blood before such transplantation. It was only after the tumor had actually been transplanted and begun its growth, that the transfusion sufficed, through the process of destroying the tumor, to give the animal immunity against further inoculation.

Digitized by Google

Perhaps the most plausible explanation of this is found in the suggestion that the transfused blood contained corpusclar or enzymic substances that could begin the decompounding of the cancer cell, and that through such decompounding a stimulus was given to the blood-forming organs of the animal that led to an elaboration of the defensive mechanism that would not otherwise take place. The permanent modification of the conditions in the dog's system that made it resistant to future inoculation would thus be attributable to activities stimulated by the cancer proteins, acting virtually as autologous antigens.

In this view, immunity thus induced is closely comparable to immunity induced by inoculation with autolyzed tissues.

The "Rational Treatment of Cancer"

No doubt it has occurred to a large number of workers, that, as Dr. Levin phrases it, "to induce an immunity to cancer growth may indicate the way to rational treatment of cancer, since such an immunity would prevent the occurrence of metastases, after the primary tumor is removed." But doubtless most such workers have felt, as Dr. Levin felt, that "it is self-evident that the results obtained cannot be transferred as yet to human pathology."

Had it occurred to any one, however, that the active agent involved was merely protein matter as such, and not enzymes specifically associated with or antagonistic to the cancer cell, there would have been no such embargo on transferring the research to human pathology.

It was familiarly known that it is possible to inoculate the human subject with foreign proteins without harmful results, as in the use of diphtheria anti-toxin, the various vaccines, and the anti-thyroid serum. As it chanced, however, the solution of the matter, or at any rate an important step in the direction of a solution, was to be found not through the application of inductive reasoning along this line, but by the empirical administration of a remedy containing vegetable proteins, namely, the original Autolysin. Clinical observation of results obtained with this remedy led to the taking up of the problem on its scientific side.

The story of this development has been told in earlier chapters. I wish now to call attention to some very recent clinical observations regarding an attempt at a "rational treatment of cancer" along lines suggested by the immunization experiments, which appears to give support, in a highly gratifying manner, to the central thesis of the present monograph, as regards the theoretical action of proteantigens on one hand and their practical utility in the treatment of cancer on the other.

Digitized by Google

Thus it is of peculiar interest to note the recent work of Klinger in the treatment of cancer with autolyzed animal tissues as published in the *Correspondenz-Blatt für Schweizer Aerzte,* September 23, 1916. A lengthy summary of the article appears in the *Journal of the American Medical Association* for November 4, 1916. No one could fail to note the similarity of the description of Klinger's results with his autolysates to our previously published reports of results obtained with Autolysin. For example, he says, as condensed in the *Journal of the American Medical Association:*

"Quite a number of cases have been reported of complete cures or essential improvement under Autolysate treatment of previously inoperable cancer. In Bertrand's case an extensive recurrence of a mammary cancer was completely cured. On suspension of the treatment after several months of daily injection, the tumor began to grow again. The resumption of growth on suspension of the treatment apparently shows that the cure was not a spontaneous subsidence of the tumor but was actually the work of the treatment. Such brilliant results are exceptional. But even in the only improved cases the inflammatory infiltration may subside and the tumor may cast off necrotic masses, the edge of the ulceration healing over. Cancers bleeding and suppurating profusely, may have the bleeding and secretion arrested. The tumor often grows so much smaller that the esophagus or the rectum may become permeable once more. Pains caused by the infiltration subside as this retrogresses. In many cases the growth becomes operable after a few weeks of autolysate treatment."

All this, obviously, might have been written of the effects of administering the vegetable proteins of Autolysin instead of the animal proteins of the autolysates. Note also the following:

"Klinger regards intravenous injection as the most effectual route. There does not seem to be any danger of an anaphylaxis, he says, but sometimes the autolysates seem to lose their power. This can be avoided by changing the material."

The striking analogy here with what has been pointed out in detail again and again in the present monograph about wearing out the effect of one proteal and changing to another will be obvious to every reader. Even more striking are the analogies suggested by the theoretical explanation offered as to the action of the autolysates, as follows:

"The results of Klinger's own research and experience confirm the possibility of influencing the growth of a tumor by injecting certain products of the breaking down of albumin. These autolysates supply the body with ready-made ferment while at the same time exerting a stimulating action on the blood-producing tissues, whipping them up to increased production of the tumor cell-destroying substances. As cancers consist essentially of albuminoid substances, it seems evident that their retrogression and

Digitized by Google

absorption depend on the intensification of certain disintegration processes."

Here, it will be observed, the ideas which furnish the essential thesis of the present monograph—to the effect that protein antigens stimulate the blood-producing tissues, and that these in turn produce the substances that destroy the tumor cell—are stated as if they were matters of common or accepted knowledge. If Klinger reached these conclusions independently, and without having seen my papers of October and November, 1914, and October 2, 1915, his estimate will obviously have peculiar value by way of corroboration.

I mention this, not because questions of priority have considerable significance or even interest, but because the main thesis involved has vast importance, and because the judicious reader cannot fail to be impressed by the fact that certain Swiss physicians working with animal proteins should have obtained results so strikingly in accordance with results obtained by American physicians working with vegetable proteins. That the name autolysate should have been applied to one proteantigen and the name autolysin—differing only by a single syllable—to the other is a matter of minor coincidental interest.

It should be explained, however, that the word "autolysate" refers to the partially autolyzed (hydrolyzed) state of the proteantigens themselves; whereas "autolysin," as the reader is aware, is merely a convenient appelation suggested by the fact that the remedy may cause the seeming autolysis (hydrolysis) of cancer tissues. It does not appear that Klinger recognizes the response of the blood-forming organs as essentially a protein reaction, but neither was the action of autolysin at the outset thus interpreted, although its capacity to stimulate the activities of the cytogenic apparatus was early recognized.

Theory of Leucocytic Action

When the original Autolysin compound had been made available for hypodermic use, it was tested by Dr. Beebe at the Loomis Laboratory on sarcomatous rats. It was then observed that, when the rat sarcoma regressed under influence of the treatment, a very notable leucocytic invasion was demonstrable in the immediate region of the tumor. A differential count was not made at this time, that phase of the problem not having gained the prominence it afterwards attained; but it was noted that the leucocytic invasion involved a relatively large lymphocytosis. Thus the results observed when a rat sarcoma regressed under influence of Autolysin were concordant with the observations of Bashford, Da Fano, and their associates in observations on mouse tumors.

Digitized by Google

At a later period, when blood tests made with the human cancer subject at the Beebe-Williams Clinic had given new insight into the relations of the white blood cells, examination was made of the blood taken from the cancer of the human subject in comparison with the blood from the finger of the same subject. Perhaps I can best illustrate the findings by transcribing my laboratory notes on a fairly typical case. The records were made October 22, 1916.

Case No. 370. Female. Original growth an epitheloid-carcinoma of the hand, leading to amputation of forearm three inches below the elbow. Present condition, axillary metastasis with open discharging wound, malodorous if not treated, but freely granulating and with serous discharge under proteal treatment. Patient under proteal treatment since November 2, 1915. Treated with the original Autolysin and special concentrated Autolysin until July, 1916; since then with mixed proteals, including a combination of alfalfa and rape proteins, to which the response seems particularly satisfactory. Patient's general condition fairly satisfactory. There had been, however, a severe hemorrhage from wound on the 18th of October, and several hemorrhages somewhat less severe on days immediately preceding. Since the 18th, however, there has been no hemorrhage, and the patient was in satisfactory condition on October 22nd when the blood count in question was made. She was able to visit the office, coming from Brooklyn on the street car, the journey involving considerable walking, a transfer, and a ride of several miles.

Notes on blood directly from the granulating tumor under the axilla: Red corpuscles, agglutinated into straggling clots. A good many clusters of platelets, indicating a somewhat friable state of the red corpuscles. No normoblasts nor microblasts.

White corpuscles exceedingly numerous. Actual count not made, but to judge from the smear they are five or six times as numerous as in normal blood—doubtless a post-haemorrhagic leucocytosis. The white corpuscles are of two types almost exclusively:

(1) Small polynuclears, with very little cytoplasm, the nuclei extending in all directions to the bounds of the cell. Nuclei staining a bright, clear dark blue; (2) Cells mostly larger than the polynuclears, staining precisely the same shade of blue as the nuclei of the polynuclear, and seemingly granular, like the typical basophile. Existing by themselves, in ordinary blood, they would mostly be classified as basophiles. Some of them, however, are small. They seem to have no cytoplasm outside the stained matter, staining as a uniform mass, in which the granular structure is fairly obvious. Sometimes there seems to be an underlying

Digitized by Google

tone of red; or one side of the spherical cell is of reddish tint. Some of them suggest eosinophiles.

That these two types of cells do not owe their peculiarities to defects of technique in staining is shown by the presence of a few polynuclears of ordinary type, with more reddish nuclei; and a very few myelocytes and transitionals with clear cytoplasm. One very large lymphoidocyte observed, with purplish nucleus, and with cytoplasm making up a large rim of very deep blue stain.

The blood from the finger puncture (on day following severe hemorrhage) shows the following characteristics: A great preponderance of polymorphs, many of them large and with clear cytoplasm, but many more with the nuclei closely convoluted as if about to expand. In a count of two hundred cells: Two typical myelocytes. Five or six typical large monocytes. About eight per cent. dark-stained cells, large, identical with those above referred to as resembling mast cells. These are probably large monocytes or large lymphocytes but no structure is visible, the cells appearing to be opaque. They may perhaps be conventionally classified as plasina cells.

As aiding in the interpretation of this study of blood from the cancer tissue itself, it may be noted that the blood of this patient, taken from the finger, a month earlier (September 19, 1916), showed 58.4 per cent. polynuclears; 30.0 per cent. large monocytes; only 5.8 per cent. small lymphocytes; and 5.4 per cent. eosinophiles. Nine months prior to that (January 8, 1916), the record was: polynuclears, 77.5 per cent.; large monocytes, 15 per cent.; small lymphocytes, 6.5 per cent.; eosinophiles, 2.5 per cent.

The most plausible interpretation of the anomolous cells observed in the blood from the tumor, a certain number of which were also found in the blood from the finger tip, is that they were large lymphocytes or large monocytes that had become engorged with tumor detritus so that their entire cytoplasm took on a basophile stain. One is led to suspect that the white cells described by Da Fano as "lymphocytes" may have been more or less of the same character. It is to be observed, too, that the polynuclear cells in the tumor were for the most part small, lacking in cytoplasm, and with closely convoluting nuclei, suggesting Da Fano's polynuclears "undergoing degeneration."

Let me supplement these observations of matters of fact with a very brief suggestion as to a possible interpretation of the observed condition. The suggestion is, of course, tentative only, but it may serve as a guide for future observation.

The suggestion I make, in the light of the Proteomorphic Theory, is this: When a cancer is undergoing regression, either spontaneously in the case of an animal or under treatment in

Digitized by Google

the case of a human subject, the observed aggregation of polynuclears is not primarily for purposes of phagocytosis, but for the secretion of polynuclear enzymes that begin the hydrolysis of the more susceptible cancer cells. The individual polynuclears themselves, actively stimulated to perform their secretory function by presence of the cancer cells, become temporarily or permanently "degenerated." Meantime the mononuclear cells, and in particular the large monocytes, accumulate in the region of the tumor, and attack the partially hydrolyzed cancer tissues, ingesting them either by phagocytosis or by absorption. That red cells also are abundant in the region of the tumor is shown by a very commonly observed condition of cyanosis of the skin overlying a superficial mass; and according to the thesis of the Proteomorphic Theory, the presence of these cells would be important to provide for the final hydrolysis of end products of protein decomposition.

The reader of this monograph will not need be told that, in my view, one of the most important features of the conditions thus theoretically explained is the presence of a relatively large number of large monocytes. Polynuclears are always relatively abundant in human blood, and lymphocytes usually are present in adequate quantities. But it would appear that these, by themselves, are not competent to deal with the entire process of dissociation and removal of the cancer cell. Only when the large monocytes are stimulated to appear in significant numbers is the equipment for the removal of cancer cells competent to overmaster the lawless growth. So the most important guide to treatment, as I have repeatedly pointed out, would appear to be the differential blood count with particular reference to the percentage of large monocytes.

I shall point out in another connection that it is necessary to consider not merely the quantity but the quality of the large monocytes. These may be lymphoidcytes, myelocytes, or leucoblasts; and these do not serve the same function, apparently, as the two types of normal large mononuclears, namely, the large lymphocyte and the typical large monocyte with basic cytoplasm. Only when the latter appear in relatively high percentage are we justified in feeling that the treatment is accomplishing all that could be desired, and that the case is progressing, or is likely to progress, favorably. But as to this, I shall speak more in detail in another connection.

The Red Corpuscles and Final Proteolysis

I shall have occasion also in a later chapter to deal more at length with questions pertaining to the red corpuscles. Considering that these form the essential theme of the most novel and

Digitized by Google

original part of the Proteomorphic Theory, it may appear that they had been somewhat neglected in the present monograph. It will be understood, however, that the red cells are supposed to be incessantly active, co-operating with the leucocytes, and completing the work of hydrolysis of the decompounding cancer proteins. In the original exposition of the Proteomorphic Theory, in *American Medicine* of October, 1914, the matter was stated as follows:

"The leucocytes, like the organs that produce the digestive ferment of the intestines, act on the full-size protein molecule, and begins its cleavage. But in the light of the new evidence, it may somewhat be doubted whether the leucocyte is able to carry on this cleavage to its final conclusion. It is at least possible that the protein molecules, multiplied by cleavage, acquire an osmotic pressure that causes the disruption of the leucocyte when the polypeptid stage of hydrolysis has been reached. If such is the case, the autolyzed leucocyte would discharge its contents in the midst of myriads of red blood corpuscles capable of taking up the work of hydrolysis where the leucocyte left it, and completing the cleavage of polypetids into amino-acids.

"According to the hypothesis already expounded, it would be only comparatively small quantities of foreign protein that would thus come under the auspices of the leucocyte; but it is not unthat considerable quantities of polypetids may find their way hablikely that considerable quantities of polypetids may find their way habitually into the blood stream; and it is to be recalled that the red corpuscles, marshalled in numbers a thousand times as great as the numbers of leucocytes, should be able to deal with the polypetids in almost any quantity.

"It is even conceivable that all the protein foodstuffs are absorbed in this state (since the evidence for their change into amino-acids in the intestinal wall is not quite conclusive), and normally undergo their final stages of hydrolysis under influence of the erythrocytic enzymes; the tissues of the liver and brain and muscle standing guard meantime in the background, as it were, ready to attack (each within the limits of its capacity) any portions of polypetids that escape the militant army of red corpuscles. The numbers and aggregate bulk of the red corpuscles suggest their possible capacity to accomplish such a task."

Such ascription to the red blood corpuscles of the function of cleaving polypetids into amino-acids, as originally stated in the monograph on the Proteomorphic Theory, has been thought by some critics to constitute an over-bold assumption. Be that as it may, it is obviously a matter of genuine interest to ascertain whether the red corpuscles have such a function; so peculiar importance attaches to a report on the distribution of the residual nitrogen between the blood cells and the plasms recently published in the *Biochemische Zeitschrift,* as reported in *Physiolog-*

Digitized by Google

ical Abstracts (published by the Physiological Society of Great Britain and Ireland with the co-operation of the American Physiological Society) in the issue of October, 1916. The experimenter was Dr. Ivar Bang. The abstract is as follows:

"The residual and urea nitrogen in the blood and plasma were determined in well-nourished rabbits before and after a seven-day fast during which no water was given. The amino-acid fraction was represented by the difference between the residual and urea nitrogen. In accordance with the findings of earlier experiments, an increase in residual nitrogen occurred after the fast which concerned the urea fraction only. Before the fast urea was equally distributed between the cells and the plasma, while the cells were richer than the plasma in amino-acid; these relations persisted after the fast.

"After the introduction of a solution containing two to three grams of glycine into the bowel, there was an increase in the residual nitrogen of the blood, which affected the amino-acid fraction almost exclusively. The increase was confined to the plasma, and hence the amino-acid content of the blood cells is probably formed in the cells themselves."

It will be observed that "blood cells" as a whole are here referred to, with no specific reference to the red cells. But the fact that the latter are about one thousand times as numerous as the leucocytes, constituting the main bulk of the formed matter of blood, makes it highly probable that the amino-acids in question were contained very largely at any rate in the eryphrocytes.

Such experimental proof of the completion of protein hydrolysis in the corpuscles is interesting from a theoretical standpoint, but doubly so from the practical standpoint of the physician administering proteins in the treatment of cancer. There remains little doubt that the red corpuscles are an essential part of the mechanism through which the cancer proteins are ultimately reduced to innocuous amino-acids.

It becomes necessary, then, to watch the red corpuscles no less than the white ones as an aid to the interpretation of the patient's progress. Not merely their numbers but their qualitative conditions should be considered—the presence of normoblasts, megaloblasts, poikailocytes, crenated and friable cells, and the like should be closely observed, as giving clues to the regulation of dosage, a change of frequency of administration, or a modification of the type of proteal employed.

The fact that Autolysin produces rapid and significant modifications in the number and character of the red cells has been too frequently observed to be matter of doubt. Statistical evidence as to this in reference to cases at the Beebe-Williams Clinic has already been presented (see the various blood-count charts).

Digitized by Google

Records of independent observers, fully confirmatory in character, will subsequently be presented.

Meantime, by way of comparison, and in anticipation of fuller discussion elsewhere, I may cite here a recent case at the Beebe-Williams Clinic, in which there was chronic protein (intestinal) toxaemia in which the red cells had the qualitative features of pernicious anaemia, although not reduced in numbers as in full development of that malady; and in which there was pronounced leucocytosis, with embryonic (ontogenetic) types of cells suggesting a leukaemic tendency. A typical count before treatment showed 3,850,000 red cells (crendated, vacuoldated, anocytosis, poikeilocytis, pronounced chromophilia, normoblasts, megalocytes); very few platelets; and 57,000 leucocytes, with 70.6 per cent. polynuclears, full cytoplasm, feebly granular, non-acidophile); 21.6 lymphocytes (mostly small and very basophile); 5.4 per cent. large mononuclears (one-third lymphoidocytes); 2.6 per cent. eosinophiles. After six days of Autolysin treatment (four doses of 4 to 8 minims, hypodermically into arm), red cells advanced to 5,012,000 in number and much less adnormal in appearance; normoblasts exceedingly rare, some groups of platelets; number of white cells reduced to 5,100, with 51 per cent. polynuclears, 30.5 per cent. small lymphocytes, 14 per cent. large mononuclears, 2.5 per cent. eosinophiles, and 2 per cent. basophiles. Patient's general condition and subjective symptoms very markedly changed for the better, as might be expected. An attempted explanation of the remarkable changes, with further history of the cases and detailed study of the qualitative condition of the cells, will be introduced in another connection.

The Value of Early Treatment

Among the most important of the observations of the animal experimenters, in their possible application to the human subjects, are those showing that (1) there is a marked distinction to be drawn between the original susceptibility of an animal to inoculation with cancer and the resistance to growth of the tumor in the same animal at a later period; and (2) the correlated fact that the same tumor appears to develop increasing virulence as it is brought through section and transplantation from the body of one animal to another.

As illustrating the first point, it is noted that a pregnant mouse is very insusceptible to inoculation with a tumor transplanted from another mouse, yet once the transplantation has been successfully effected, the tumor grows with extraordinary vigor.

A possible explanation of this would be that the pregnant animal has a system relatively well fortified against protein invasion,

Digitized by Google

due to the fact that there is a certain amount of proteid absorption from the placenta (the experiments of Abderhelden in this connection will be recalled), which led to a leucocytosis, and to the presence of an increased enzyme titer in the blood. In a word, the organism is well equipped to fight against the invasion of the protein cells represented by the cancer inoculation. If, however, in spite of this condition of preparedness, the cancer cells grow with such vigor that they prevail against the defending host, then it is not surprising that they take on very rapid development, because of the relatively large amount of nourishment that must be present in the blood and lymph channels of the pregnant animal to provide for the growth of the embryo.

It will be recalled that investigators have shown the chemical affinity between the rapidly growing tumor and the embryo—each of them containing a relatively low nitrogen content. In a sense, the foetus is in itself a foreign tumor, and one that takes on extraordinary rapidity of growth. Like the malignant tumor, the foetus has capacity for almost indefinite growth; and were it not possible presently to extrude the foetus it would become as great a menace to the life of the mother as the cancer itself. That thought need not be expanded here, however. From the present standpoint, the important thing is to recall that there is a distinction between the initial resistance to the early growth of a tumor and subsequent resistance to its later growth.

It is probable that this variation is not due solely to conditions in the system of the animal, but that it is also dependent in part on changed conditions of the tumor itself. This idea finds strong support in the observed increasing virulence of tumors as they pass from one organism to another. It seems plausible to suppose that this increasing virulence is at least in part a function of age; and to infer from this that cancer tissues in the same individual may gain increasing virulence as they grow older. The familiar fact that cancer cachexia appears only at the later stage of development of the malady in the human subject; coupled with the fact that metastatic secondary tumors very commonly grow with exceptional vigor, gives added support to this suggestion.

The obvious application of this line of reasoning is that there is an enormous premium on early treatment of cancer in the human subject—not merely treatment in the sense of cutting out the new growth as soon as it is discovered—though in many cases that may be desirable—but also in the sense of fortifying the defensive mechanism of the body by every available means. There is abundant clinical warrant for the belief that the protein treatment, for example, may accomplish results when administered to a patient having a new cancerous growth that could not be hoped for were the tumor a post-operative recurrence; the obvious ex-

Digitized by Google

planation being, in the light of what has just been said, that, on one hand, the new tumor is probably relatively non-virulent and, on the other hand, that the system of the patient has not had time to undergo so profound a condition of metabolic disturbance as accompanies the progress of the malady.

An illustration of the force of this line of reasoning is furnished by a letter that chanced to come to hand on the day when this chapter was being revised for the printer. The letter comes from a physician in Vera Cruz, Mexico, and bears date of October 12, 1916. It is well worth transcribing in full:

"In accordance with your request, I am sending you a report on my first case with Autolysin.

"———— ————, age thirty-two, a Mexican, came to my office about six months ago to consult with me. On examination I found she had a small nodule or tumor about the size of a bird's egg and about one and one-half inch below the nipple of the left breast. She was complaining of some pain at that time. She consulted me three or four times during the past six months and each time I noticed that the tumor was getting larger.

"At the two last examinations the tumor had become as large as a hen's egg—very hard; with pains radiating up to the shoulder and chest; with enlargement of the axillary glands.

"I had no apparatus at hand to make a microscopical examination; but diagnosed it as cancer of the breast.

"On September 12th I gave one c.c. Autolysin in the subcutaneous tissue of the arm, with slight reaction in two hours.

"The other injections were given on the following days: 13th, 14th, 15th, 16th, 17th, 18th, 19th, 21st, 23rd, 25th, 27th. After the second injection, pain subsided, and at each succeeding injection the tumor became softer and smaller, and at the last examination, October 6th, the tumor had entirely disappeared together with the enlargement of the axillary glands.

"At this date, October 12th, the patient seems perfectly well and is going about her duties quite happy and contented.

"I am very much enthused over the results obtained."

Here, it will be observed, regression of the rather rapidly growing tumor began after administration of a very few doses of Autolysin, and continued with striking rapidity. Such a result could not be expected had not the defensive forces of the body been in fairly good working order, so that only a relatively slight additional impulse was necessary to enable them to over-master the cancer cells.

It will be peculiarly interesting to observe in future whether such a case as this is immune to the recurrence of cancer. It would appear that such a hope is not without warrant, considering the well-recognized immunity of animals to second inoculation after regression of a tumor. It must not be overlooked,

Digitized by Google

however, that there are radical differences between transplanted and spontaneous tumors.

It must be obvious that one could not hope for so striking a result as that just outlined in any very chronic or recurrent case of cancer. What the Mexican physician accomplished in a period of two or three weeks would require a term of months in a case at a later stage, in which the cancer cells were additionally fortified and the bodily defenses progressively weakened. Stimulated by the presence of the abnormal cells, the blood-forming mechanism may ultimately reach a point of exhaustion which permits only a feeble response to new proteins. Myelocytes, leucoblasts and lymphoidocytes take the place of normal large monocytes; normal polymorphs are replaced by those of small, immature type; the lymphocytes are devoid of cytoplasm—a "starved" type; the red cells poikilocytic or nucleated.

This, assuredly, is not a hopeful picture. Yet even under such circumstances modifications in the blood in the direction of normality, and corresponding improvement in the general condition of the patient, together with modifications of the neoplasm, are sometimes effected by protein treatment within a relatively brief period, though not with spectacular suddenness. In one of our recent cases (No. 488), for example, a recurrent cancer of the breast rapidly developing about one year after removal, the blood count before treatment showed 33 per cent. of large mononuclear leucocytes, but very few of these were normal monocytes, the major part of them being of the leucoblast type. In the same count the polynuclears represented 53.3 per cent. and the small lymphocytes only 8 per cent., the eosinophiles 4.9 per cent.

After five days' treatment with rape protein, there was a very remarkable transformation. The leucoblasts had disappeared, possibly being transformed into polynuclears, since the latter now represented 69 per cent. of the white cell count. Large mononuclears were now only 4.6 per cent., but these were of the normal type, either of true monocytes with large nucleus and basic cytoplasm or of Ehrlich's transitionals. Meantime, there had been, seemingly, very active stimulation of the lymphatic system, since the small lymphocytes now numbered 23.5 per cent. Many of the lymphocytes were fairly large, and with a relatively large amount of cytoplasm. The eosinophiles were now only 1.5 per cent., but there were granular cells that stained dark, resembling the eosinophiles in structure rather than true basophiles, to the additional number of 4.3 per cent.

After another interval of five days, the leucocyte count had progressed still farther in the direction of normality, as regards the quality of the cells, the typical large monocytes now numbered 7.2 per cent.; the polynuclears 60.2 per cent.; lymphocytes

Digitized by Google

24.4 per cent.; eosinophiles 5.6 per cent.; basophiles 1.2 per cent. At this time study of the red cells showed a great abundance of normoblasts and free microblasts. Two weeks later, however, these had altogether disappeared (October 18th). The large monocytes, of normal type, now numbered 9.6 per cent.; the polymorphs stood practically unchanged at 59.6 per cent.; the lymphocytes had fallen to 19.6 per cent., and there were only 1 per cent. each of eosinophiles and basophiles. A month later (November 16th), the count showed continued progress, the polynuclears having fallen to 55.3 per cent., whereas large mononuclears had risen to 13.3 per cent., small lymphocytes to 27.3 per cent., and eosinophiles to 4 per cent.

The significant feature of this blood modification was the transformation from abnormal types to normal types of large mononuclears and the very notable increase of lymphocytes. The patient's general condition had meantime improved and there was a tendency to softening of the tumor mass in the breast, flattening of a large lymph node in the axilla, and marked regression of a subclavicular mass. It was not to be expected, however that very marked regression of the tumor would occur until the large monocyte count had been brought to a much higher state. The ultimate result must be left for future record. I mention the case here merely to illustrate a rather exceptional modification of the blood count, and to emphasize the point that in a case of such chronicity, in which the lymphatic system is seriously involved, with metastases, one must be content to go slowly, expecting no such spectacular metamorphosis as was recorded in the letter above quoted.

By way of contrast, note the progress of another recent case (No. 497) in which there was primary involvement of both breasts not far advanced. A surgeon had advised removal of both breasts, yet malignancy was considered doubtful by us until the blood count showed the following: polynuclears, 48.9 per cent.; large mononuclears (including myelocytes), 16.6 per cent.; small lymphocytes, 30.5 per cent.; eosinophiles, 4 per cent. The response to the proteal treatment was immediate; the patient reported a transformation in general health, and the blood count after three weeks of treatment (November 16, 1916) was: polynuclears, 43.6 per cent.; large monocytes, 21 per cent.; small lymphocytes, 33.6 per cent.; eosinophiles, 1.6 per cent.

The rapid response of this patient as contrasted with the preceding one may be ascribed, in all probability, to the early stage of development of the neoplastic growths.

With the emphasizing of this point, I may perhaps advantageously leave this aspect of the subject, reiterating the opinion that: here, as in so many other fields of pathology, there is a tremen-

Digitized by Google

dous premium on early treatment. Proteal remedies have indeed proved capable of giving solace in extraordinary measure to late stage inoperable cases of the most hopeless type; but the full measure of what may be expected of the new treatment can be gauged only when the remedy has been administered to a large number of cases at an earlier stage of development.

SECTION XI

THE PREVENTION AND CURE OF CANCER

If the essential thesis of this paper as to the nature of cancer is accepted, and it is further accepted that the administration of vegetable proteins hypodermically tends to stimulate the enzymes capable of protein hydrolysis, certain practical suggestions as to the prevention of cancer; as to possible cure of the cancerous condition; and as to the obviation of its recurrence, follow almost as matters of course.

Since, however, things that seem obvious after one has devoted much thought to a subject are not always quite so plain to those who have thought along different lines, perhaps it may not be amiss to present here, partly by way of summary and recapitulation, a brief practical discussion of the prevention and the possible cure of the condition which I have characterized as hyperproteomorphism, with particular reference to that phase of the condition characterized by the presence of a malignant neoplasm or true cancer.

As to prevention, I shall speak only in the briefest terms. Whatever tends to maintain the general good health, keep the blood count normal, promote the normal digestion and nutrition, and keep the muscles (including those of the arterial walls) plastic, tends to ward off the cancerous condition.

No single expedient, in my judgment, is more important than habitual and vigorous exercise, particularly for persons in middle life and (modified in intensity) in old age. Keep the muscular system in really vigorous condition; avoid excess proteins in the food, in particular animal proteins; drink plenty of water; avoid all sources of general systemic irritation as well as local irritation, and there is at least a large measure of probability that the cancerous condition will never develop.

Once it has developed, however, and in particular when it has formed a local neoplasm of the type that we term epithelioma, carcinoma, or sarcoma, as the case may be, is there a possibility of a cure of the condition?

Digitized by Google

The answer must be, I think, that there is nothing inherent in the nature of the malady that makes it necessarily fatal (the results of animal experimentation appear to justify this verdict); but that, on the other hand, it is implied in the very nature of the condition that unless there can be a radical readjustment of the relations of the individual to his environment, the case is hopeless.

Merely to cut out the local neoplasm, and hope thus to cure the disease, is a childish procedure. The surgeon tells you that if you make the incision early enough and radical enough, all will be well. But, of course, you can never make the incision early enough nor radical enough. You could, to be sure, eradicate cancer of the uterus by universal hysterectomy in childhood, and annul cancer of the breast by universal amputation of infantile mammae. But such a procedure would have no conspicuous bearing on the cancerous condition, and would not in any way shield the organs that remained.

It is true that most surgeons claim a considerable proportion of "cures" following their operative procedures, particularly for cancer of the breast. But very few surgeons have cared to publish statistics as to the post-operative history of their cases, extending over a term of years. One surgeon of my personal acquaintance admits that when he attempted to follow up his cases he found that very few indeed were living three years after the operation, and only a single case after a lapse of five years.

Whether or not we accept that as a typical experience, it will be denied by no one that the usual and, so to say, expected history of a cancer case after operation is characterized by metastatic recurrence; that after a second and perhaps a third operation the case reaches an inoperable stage; and that inoperable cancer is universally regarded as among the most hopeless of conditions.

Speaking with the utmost conservatism, we can now say that experience justifies the statement that the Autolysin treatment has come with at least a message of hope for these supposedly hopeless cases. As regards actual and permanent eradication of the diseased condition, doubtless this applies to only a small percentage of the cases hitherto treated by the new method. But that is merely equivalent to saying that the major part of the cases thus treated have been individuals whose systems were in so profound a state of disrepair that in the nature of the case they could not be mended.

Researches at the Mayo Clinic have made it clear to what an alarming extent changes that may be considered cancerous in character occur in other organs of the body than those directly effected either by the original neoplasm or by definite metastases.

Digitized by Google

These observations are obviously in keeping with the present thesis as to the general character of the cancerous condition. They accord also with a wide range of clinical experience. It is almost axiomatic to say that no two cases could be precisely alike as to the exact degree of involvement of the various organs and tissues of the body. Inherent susceptibilities of hereditary character, combined with accidental conditions of local irritation, would determine that in one case the liver, in another the pancreas, in a third the kidneys would have suffered most from the condition of nutritional maladjustments, in a series of cases in all of which the seat of the "primary cancer" might be, let us say, the breast, the stomach, or the uterus.

It is equally axiomatic to say that the precise location of metastatic masses and the precise relative degree of involvement of various organs affected without metastasis must be vastly important in its bearing on the prognosis of the case as regards imminence of the fatal issue.

Obviously, then, each case must be a law unto itself. If it is hazardous to generalize regarding conditions described merely as "cancer of the breast," "cancer of the uterus," etc., it is equally hazardous to attempt predictions as to the possible curability of any individual case thus described.

No one speaking with authority in connection with the Autolysin treatment ever made such a prediction or held out the expectation of cure in any individual case.

Dr. Beebe has repeated in every paper he has published that he made no suggestion that the new remedy is a "cure" for cancer.

No one speaking with authority has suggested or expected that the remedy would perform the necromantic feat of restoring degenerated and decompounded cells of liver or spleen or kidneys or pancreas or intestinal glands. As well ask the surgeon to replace a lost arm or leg. Yet without such regeneration, in a large proportion of cases, it would be utterly futile to hope for the restoration of normal conditions of protein metabolism absolutely essential to health.

If, in such a case, the Autolysin treatment favorably modified the blood count and made possible a temporary improvement in metabolism; thereby relieving the patient's distress; nullifying the obnoxious odors of cancerous discharge, inducing a sense of well being, and prolonging life by a term of weeks or months while at the same time giving comfort—everything has been accomplished that could rationally be expected; everything, perhaps, that can ever be hoped for in connection with the treatment of cases at so advanced a stage.

It should be added, however, that it is seldom possible to determine with accuracy the precise stage of advancement of any

Digitized by Google

given case, for the obvious reason that we cannot examine the structure of the various organs even if quantitative tests of their degree of involvement were available. A case that seems profoundly cachectic, and even almost moribund, may in reality have tissues less vitally involved than those of another case that has been tangibly affected for a much briefer period and in which the visible symptoms seem less alarming.

Hence it occasionally happens that a case in which the most optimistic estimate of a skilled observer would predict a very early demise responds to the treatment with unexpected vigor and rallies in a way which enthusiastic observers have not hesitated to speak of as "almost miraculous."

In a considerable number of instances, cases of this character have gone on, under the Autolysin treatment, to a stage of improvement which may with validity be spoken of as clinical recovery. Whether or not the conditions of bodily metabolism have been permanently readjusted in such wise that the proliferation of mis-placed cells will be prevented in future, must be left to the future to decide.

It may fairly be said, I think, that where a cancerous mass has thus retrogressed under the Autolysin treatment there is greater inherent probability of non-recurrence than if it had disappeared under local treatment or through surgical interference; inasmuch as an improved condition of general bodily metabolism is implied in the results attained by the hypodermic method.

When treatment consisting exclusively of hypodermic injection into the tissue of the upper arm has resulted in the regression of a tumor mass in the pelvis, no argument is required to show that there has been profound modification of the condition of the body fluids. It is perhaps permissable to hope that this modification may have an element of permanency, or that it may be kept up by occasional administration of the hypodermic remedy, and that recurrence or metastasis of the localized cancerous mass will thus be prevented.

I repeat, that this is a matter for the future to decide. But I would suggest also that every practitioner who has successfully treated a case with Autolysin should feel it incumbent upon him to urge his patient to have a blood count made at intervals of two or three months so long as he lives, and to submit himself to a new course of treatment should the blood show the slightest deviation from the standard. Doubtless it would be safer to take an occasional course of the treatment whatever the blood conditions. In any event, the treatment should not be discontinued for a good many weeks after the disappearance of the neoplasm.

That there should be most careful attention to the diet with particular reference to the nitrogen balance, goes without saying.

Digitized by Google

Careful attention should be given to all hygienic measures tending to promote general health. But in particular a régime of life should be adopted that includes daily systemic exercise of the most vigorous type consistent with the patient's condition of muscular tract. In my opinion, no single measure is more important than this; indeed, no other measure except that concerning the protein diet, approaches it in importance.

But these, after all, are matters regarding which the wise physician scarcely needs counseling. When it is clearly apprehended that the cancerous condition is due to a maladjustment of protein metabolism, it follows as a matter of course that all the measures commonly recognized as tending to reestablish the normal adjustment of such metabolism must be, in the first instance, preventative of cancer; in the second instance, invaluable as auxilliaries during the treatment of the malady, by whatever method; and, in the third place, indispensable as measures directed against recurrence of the malady.

But while all this, stated in general terms, seems fairly axiomatic, there goes with the suggestion the implication that no type of malady could give greater opportunity for the exercise of professional skill than the treatment of the cancerous condition. I have urged the futility of surgical treatment which is content merely to wield the knife and disregard all general measures. I would now urge that it would be only a degree less fatuous to suppose that adequate treatment of a cancer case by the protein method implies merely the random administration of a hypodermic. Yet a good many physicians who have used the remedy have seemed to labor under this misapprehension. The correspondence is filled with letters from physicians of acknowledged standing who state that they have administered a dozen ampules, or two dozen ampules, of the remedy with remarkable results, and who now wish to ask if it is necessary to continue treatment.

A typical instance of this kind concerned a case of uterine cancer, originally operated upon and, after recurrence, pronounced inoperable at one of our most important metropolitan cancer hospitals; and subsequently radiumed without benefit and pronounced hopeless. Autolysin had been turned to as a last resort, and eighteen doses had been administered in a term of about six weeks. And then the physician, without show of emotion, calmly inquires whether there is any necessity for further treatment,—a cure having seemingly been effected!

Needless to say the physician was urged to continue the treatment. He did continue it, and at the time of the present writing (a year later) the condition of the patient is still in the highest degree satisfactory.

I cite this instance as illustrating how vague may be the con-

Digitized by Google

ption of the true character of cancer in the minds of well-informed physicians. Perhaps this is not surprising, considering that the available authorities differ so widely in their estimate of the nature of cancer. The fact that Metchnikoff advocated the theory of the germ origin of cancer no doubt has had great weight; and doubtless there are physicians who, in accepting this new, and having also in mind the conceivability of destroying disease germs at a single dose, or at the most with two or three doses, as was at first expected of Salvarsan, have thought that proteolysin might act in similar manner. Their expectations seem to be justified when the administration of two or three doses produces very striking modification in symptoms, including change in the character of the discharge, and a softening and tendency to regress in the neoplasm itself.

Even were cancer a germ disease (which I altogether disbelieve), and were it therefore possible to conceive a treatment that would eradicate the cause of the disease at a single coup, by the slaughter of bacteria, there would still remain the neoplasm itself, a proteid mass, to deal with. To expect that medication of any character would lead to the dissolution of the mass, when it is a large one, without profound systemic disturbance would be to misconceive the nature of the essential psyiological conditions. It is neither to be expected nor desired that the protein matter making up the cancer should be hydrolyzed all at once, nor even with great rapidity. Were the enzymic attack on the cancer cells so active, the blood must become charged with the products of protein decompounding, and a tax would be put upon the cerebral tissues and the organs of elimination that they might not be able to withstand.

It follows that the carrying of a case of cancer under the proteal treatment to a favorable issue, even in the least complicated cases, is a matter demanding full measure of professional skill. I recall once hearing a somewhat distinguished artist say that anyone can *begin* the painting of a picture, but that it takes an artist to *finish it*. Similarly it may be said that any one can begin the proteal treatment of a case of cancer. Whoever can administer a hypodermic with ordinary aseptic precautions can secure definite results that are conspicuous and even notable in a great majority of cases. But to carry the case forward so that the effects are cumulative, and ultimately to secure the largest measure of benefit possible, requires skill of a high order.

If the best possible results are to be attained, it will be necessary not only to administer the treatment with constant observation of results as a guide to dosage and frequency of administration and the shifting from one proteal to another; but also to invoke, in many cases, the aid of supplementary measures.

Digitized by Google

First and foremost among these supplementary measures, is the knife of the surgeon. It is true that Autolysin has hitherto been applied almost exclusively in inoperable cases. But in more than one instance it has happened that, under the influence of the remedy, a cancerous mass too widely extended for removal has regressed until the remaining mass is readily operable. In such a case, I would strongly urge that the co-operation of the surgeon should be sought, and the mass excised. By so doing, we relieve the system of the patient of the burden of absorption of a mass of protein tissue.

Not only has Dr. Beebe followed this procedure with gratifying results, but it has been resorted to by several independent physicians in various parts of the country. In at least one instance, the residual mass ultimately removed was subjected to microscopic examination by a foremost metropolitan pathologist. His findings, taken in connection with the history of the case, are so interesting that I cannot refrain from quoting them here.

The case in question was a cancer of the breast treated by a physician in Texas, who sent the following letter regarding it:

"I received the Autolysin and began the treatment of the patient at once, who had cancer of the breast. The results to date have indeed been gratifying both to the patient and myself. The mass has almost disappeared. I have given 12 ampules. There is a small place left about 2/3 the size of a hen's egg. Now will that continue to go away or had I better have more Autolysin?"

A few days later he wrote:

"I reported the latter part of March the results obtained from the use of Autolysin in the treatment of a case of cancer of the breast. I believe I mentioned there still remained a hard mass in the breast. Well, it still remained after using the last 12 doses you sent, so a few days ago I removed the hard mass with as much of the adjoining tissue as I could well dissect out. I can say this much for Autolysin that it hastily transformed an inoperable cancer into one that could be removed readily. Now would it not be a good idea to use another dozen doses in this case to make the case more sure of recovery? I realize that without Autolysin the case would have been hopeless in my hands."

The excised mass having been sectioned and examined by a pathologist of national reputation, not personally known to the physician who treated the case, the following report was given:

"The breast recently received from you, name unknown, has been examined with the following results:

"The breast is of small dimension, consisting of a mass of fibrous tissue beneath the nipple, 3 by 4 by 5cm, and incorporated in one portion and extending beyond this mass is an encapsulated area of yellowish apparently necrotic material 2 by 3 by 4 cm. The

Digitized by Google

is firmly fixed but not retracted. The skin about nipple
ly fixed. No cysts appear at any point.
section the hard opaque mass beneath nipple is found to
of typical fibrocarcinoma in which the cells are well nour-
mitoses not found, degeneration changes not prominent or

e yellow mass is composed of entirely necrotic tumor tissue
retains enough structure to show that it reproduces the
es and details of fibrocarcinoma. In the opaque mass of
rcinoma may be seen several areas which show various
toward the complete necrosis described in the yellow mass.
m unable to account for the large circumscribed mass of
ic tumor tissue on any other basis than that some necrotiz-
ent has been injected into this breast at various points re-
in the complete destruction and mummification of a large
n of a fibrocarcinoma. An agent acting generally would
ffected all parts of the tumor, but for the most part the
e mass under the nipple, while showing foci of necrosis is
ourished but apparently not very active fibrocarcinoma."

e, it will be observed, the pathologist makes the definite
ent, that, in his experience, nothing could have produced
crosis of cancer cells except the injection of a local necrotiz-
ent.

when the physician who administered the treatment was
gated, by letter, he replied that Autolysin had been ad-
ered solely by hypodermics *into the arm.* He added that
ision healed kindly, and that the patient was now seemingly

e, then, is fairly demonstrative evidence from the pathologi-
oratory of the validity of the oft repeated clinical observa-
at the administration of Autolysin stimulates bodily pro-
capable of decompounding the cancer cells. So the case
as double interest. I have brought it forward, however, to
size the suggestion that it was desirable to remove this
pounding tissue with the knife, rather than leave it for
l absorption.

enty-four doses of Autolysin had sufficed to bring the case
adily operable stage. Possibly a good many weeks of treat-
might have been required for the absorption of the necro-
esidual matter and the complete elimination of the remain-
rcinomatous cells.

m this and several similar experiences, we may safely draw
neral inference that wherever possible the Autolysin treat-
should be administered in full co-operation with the surgeon,
at the absorptive demands put upon the system should be re-
to a minimum by free use of the surgeon's knife. I would
y this only by saying that it is seldom necessary, in our

Digitized by Google

experience, to make the surgical operation so radical, when Auto
lysin is used, as it otherwise must be; inasmuch as the metastati
glands and the neighboring tissues—which at best the surgeo
can remove but inadequately—are peculiarly subject to the pr
teolytic enzymes invoked by the administration of the hypodermi
remedy.

It goes without saying, now that proteal therapy supplies
means hitherto not available, to stimulate the production of th
blood corpuscles and whip up their enzyme-forming capacitie
that no surgeon of judgment will think of performing an oper
tion for cancer without supplementing his surgical procedure wi
the use of proteal remedies before and for some time after tl
operation.

It should be recalled that no treatment can hope to produce be
ter general systemic conditions than the individual patient exper
enced during his normal life; hence that every one who has su
fered from cancer must always be more or less liable to recu
rence,—unless, indeed, it should ultimately be shown that a mea
ure of immunity results from regression of the neoplasm.

In other words, the cancer would not originally have develop
had there not been certain inherent defects in the bodily mec
anism of the individual. Often these defects are hereditar
Usually they are associated with the on-coming of old age, prem
ture or otherwise. They mark a condition in which the capaci
of the organism to deal with protein metabolism is waning. S
this individual will probably always need the prop of an artifici
stimulant to the cytogenic apparatus from time to time. Protea
supply such a prop. Their use will probably become routine pra
tice not only in the post-operative treatment of cancer subject
but in the after-year treatment of cases that have had the ne
plasms removed by the action of proteals themselves.

Obviously the same thing applies to cases treated successful.
with X-ray and radium.

In a word, it may be expected that the province of proteal ther
apy will be by no means confined to the *treatment* of cancer, bu
will have a place at least as important, and conceivably more im
portant, in the prevention of recurrence after the local neoplasm
has been removed by any means whatsoever; and, ultimately also
no doubt, in prophylaxis applied to any person who through mal
nutrition, combined with some local source of irritation, ha
reason to fear the development of cancer.

Meantime this method gives to the individual cancer suffere
whatever the stage of his malady, and to the physician who i
called upon to treat him, the most enheartening message of hop
that present-day therapeutics can offer.

Digitized by Google

NOV 1 30

OCT 24 1930

NOV 22

L261 Williams, H.S.
W72 The proteal
1916 of cance

NAME

M. James.

D Carter.

Digitized by Google

Digitized by Google